



STIC Search Report

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STIC Database Tracking Number: 197060

TO: Dwayne C Jones
Location: REM/3B87/3C70
Art Unit: 1614
August 4, 2006

Case Serial Number: 10/768953

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

9578
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SEARCH REQUEST FORM

Requester's Full Name: Dwayne C. Jones Examiner #: 71299 Date: 31 JUL 06
Art Unit: 164 Phone Number: 2-0578 Serial Number: 10768953
Location (Bldg/Room#): 3B87 (Mailbox #): 3C17 Results Format Preferred (circle): PAPER DISK

REM

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Type of Invention: All attached sheet

Co-inventors (please provide full names): 11

Earliest Priority Date: 11

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the named species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

* Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search claims 1, 7, 19, 20, 21, 22, and ~~23~~
claim 41 for the compound of
formula III, A₁-L₁-B₂

(circle) and the elected species of
2-(2-methylthia-3-1-4-yl)ethylpyridine (MTEP)
(claim 42.)

Jones 10_768953 - - History

=> d his ful

(FILE 'HOME' ENTERED AT 10:19:00 ON 04 AUG 2006)

FILE 'REGISTRY' ENTERED AT 10:19:20 ON 04 AUG 2006
L1 1 SEA ABB=ON PLU=ON MTEP/BI

FILE 'HCAPLUS' ENTERED AT 10:20:54 ON 04 AUG 2006

FILE 'REGISTRY' ENTERED AT 10:21:05 ON 04 AUG 2006
SET SMARTSELECT ON
L2 SEL PLU=ON L1 1- CHEM : 2 TERMS
SET SMARTSELECT OFF

FILE 'HCAPLUS' ENTERED AT 10:32:05 ON 04 AUG 2006
L3 46 SEA ABB=ON PLU=ON L2
L4 46 SEA ABB=ON PLU=ON L3 OR MTEP
L5 34433 SEA ABB=ON PLU=ON ("OVERACTIVE BLADDER"/CV OR "BLADDER,
DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7 148785 SEA ABB=ON PLU=ON L5 OR URINARY? OR ?CYSTITIS? OR URINE(2A) LE
AK? OR ENURESIS OR BED(W) WETTING
L8 1 SEA ABB=ON PLU=ON L4 AND L7
D STAT QUE L8
D IBIB ABS HITSTR L8 1
L9 45 SEA ABB=ON PLU=ON L4 NOT L8
D STAT QUE L9
D IBIB ABS HITSTR L9 1-45
L11 2 SEA ABB=ON PLU=ON PYRIDINE(L) METHYL(L) THIAZOLYL(L) ETHYNYL
L12 33 SEA ABB=ON PLU=ON PYRIDIN?(L) METHYL(L) THIAZOL?(L) ETHYN?
L13 0 SEA ABB=ON PLU=ON L7 AND L12
L14 6 SEA ABB=ON PLU=ON L12 NOT (L8 OR L9)
D STAT QUE L14
D IBIB ABS L14 1-6
SELECT RN L8 1

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201943-63-7/BI OR 329205-68-7/BI OR 57-27-2/BI OR 7370-21-0/BI
OR 96206-92-7/BI)
L16 STR
L17 3 SEA SUB=L15 SSS FUL L16

FILE 'HCAPLUS' ENTERED AT 10:54:41 ON 04 AUG 2006
L18 183 SEA ABB=ON PLU=ON L17

FILE 'REGISTRY' ENTERED AT 10:55:30 ON 04 AUG 2006
L22 628 SEA ABB=ON PLU=ON MGLUR5/BI OR METABOTROPIC(L) GLUTAMATE(L)
RECEPTOR
L23 20 SEA ABB=ON PLU=ON ANTIMUSCARIN? OR OXYBUTYNIN OR TOLTERODINE
OR DARIFENACIN OR TEMIVERINE
L24 0 SEA ABB=ON PLU=ON ADRENERGIC(L)ANTAGONIS(L) (ALPHA OR
"A") (L) 1
L25 39 SEA ABB=ON PLU=ON L24 OR PRAZOSIN OR DOXAZOSIN OR TERAZOSIN
OR ALFUZOSIN OR TAMSULOSIN

FILE 'HCAPLUS' ENTERED AT 11:38:42 ON 04 AUG 2006
L26 1150 SEA ABB=ON PLU=ON L22 OR MGLUR5 OR METABOTROPIC(W) GU
LTAMATE
L27 2191 SEA ABB=ON PLU=ON L23 OR ?ANTIMUSCARIN? OR ?OXYBUTYNIN? OR
?TOLTERODIN? OR ?DARIFENACIN? OR ?TEMIVERIN?

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Jones 10_768953 - - History

L28 16238 SEA ABB=ON PLU=ON L25 OR ADRENERGIC(W)ANTAG? OR ?PRAZOSIN?
OR ?DOXAZOSIN? OR ?TERAZOSIN? OR ?ALFUZOSIN? OR ?TAMSULOSIN?
L31 19844 SEA ABB=ON PLU=ON NEUROMUSCULAR?/CV OR NEUROMUSCUL?
L32 0 SEA ABB=ON PLU=ON (L18 AND (L27 OR L28 OR L31)) NOT (L8 OR
L9)
L33 78 SEA ABB=ON PLU=ON L18(L)L26
L34 51 SEA ABB=ON PLU=ON L33 AND (?DRUG? OR ?MEDICIN? OR ?PHARM? OR
?THERAP?)
L35 39 SEA ABB=ON PLU=ON L34 NOT (L8 OR L9)
L36 39 SEA ABB=ON PLU=ON L32 OR L35
D STAT QUE L36
D IBIB ABS HITSTR L36 1-39

FILE 'REGISTRY' ENTERED AT 11:46:26 ON 04 AUG 2006

L37 STR
L38 STR
L39 STR
L40 141354 SEA SSS FUL L37 OR L38 OR L39
L41 STR
L42 53419 SEA SSS FUL L41
L43 STR
L44 STR
L45 39484 SEA SSS FUL L43 OR L44
L46 226120 SEA ABB=ON PLU=ON L40 OR L42 OR L45
L47 226119 SEA ABB=ON PLU=ON L46 NOT (L18 OR L1)

FILE 'HCAPLUS' ENTERED AT 11:48:16 ON 04 AUG 2006

L48 42397 SEA ABB=ON PLU=ON L47
L50 30 SEA ABB=ON PLU=ON L48 AND L26
L53 222 SEA ABB=ON PLU=ON L48 AND (L27 OR L28)
L54 26 SEA ABB=ON PLU=ON L48(L)(L27 OR L28)
L55 1941 SEA ABB=ON PLU=ON L48(L) (?MEDICIN? OR ?THERAP? OR ?DRUG? OR
?PHARM?)
L56 98 SEA ABB=ON PLU=ON L55 AND L53
L60 139 SEA ABB=ON PLU=ON (L50 OR L54 OR L56) NOT (L8 OR L9 OR L36)
L61 77 SEA ABB=ON PLU=ON L60 AND PD=<OCTOBER 1, 2003
D STAT QUE L61
D IBIB ABS HITSTR L61 1-77
L62 102 SEA ABB=ON PLU=ON "LEONARDI A"/AU OR "LEONARDI AMEDO"/AU
L63 156 SEA ABB=ON PLU=ON "TESTA R"/AU OR ("TESTA RODOLFO"/AU OR
"TESTA RODOLFO H"/AU) OR "TESTA R H"/AU
L64 46 SEA ABB=ON PLU=ON ("POGGESI E"/AU OR "POGGESI ELENA"/AU)
L65 6 SEA ABB=ON PLU=ON L62 AND L63 AND L64
L66 16 SEA ABB=ON PLU=ON L62 AND (L63 OR L64)
L67 21 SEA ABB=ON PLU=ON L63 AND L64
L68 69 SEA ABB=ON PLU=ON (L62 OR L63 OR L64) AND (L4 OR L5 OR L6 OR
L7 OR L18 OR L26 OR L27 OR L28 OR L31 OR L48)
L69 75 SEA ABB=ON PLU=ON (L65 OR L66 OR L67 OR L68) NOT (L8 OR L9
OR L14 OR L36 OR L61)
D STAT QUE L69
D IBIB ABS HITSTR L69
D IBIB ABS HITSTR L69 2-75

FILE HOME

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

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Jones 10_768953 - - History

STRUCTURE FILE UPDATES: 2 AUG 2006 HIGHEST RN 898176-03-9
DICTIONARY FILE UPDATES: 2 AUG 2006 HIGHEST RN 898176-03-9

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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<http://www.cas.org/ONLINE/UG/regprops.html>

FILE HCAPLUS

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FILE COVERS 1907 - 4 Aug 2006 VOL 145 ISS 6
FILE LAST UPDATED: 2 Aug 2006 (20060802/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d stat que 18
L1      1 SEA FILE=REGISTRY ABB=ON   PLU=ON   MTEP/BI
L2      SEL PLU=ON L1 1- CHEM :      2 TERMS
L3      46 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L2
L4      46 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L3 OR MTEP
L5      34433 SEA FILE=HCAPLUS ABB=ON   PLU=ON   ("OVERACTIVE BLADDER"/CV OR
          "BLADDER, DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7      148785 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L5 OR URINARY? OR ?CYSTITIS?
          OR URINE(2A)LEAK? OR ENURESIS OR BED(W)WETTING
L8      1 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L4 AND L7
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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:648386 HCAPLUS
DOCUMENT NUMBER: 141:167823
TITLE: Selective mGlu5 antagonists for treatment of
neuromuscular dysfunction of the lower urinary
tract
INVENTOR(S): Leonardi, Amedeo; Testa, Rodolfo; Poggesi, Elena
PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica E
Farmaceutica S.P.A.
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2004067002	A2	20040812	WO 2004-EP951	20040130
WO 2004067002	A3	20041125		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI			
EP 1599204	A2	20051130	EP 2004-706676	20040130
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
JP 2006516587	T2	20060706	JP 2006-501708	20040130
PRIORITY APPLN. INFO.:			IT 2003-MI151	A 20030130
			WO 2004-EP951	W 20040130

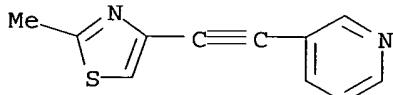
OTHER SOURCE(S): MARPAT 141:167823

AB Antagonists that are selective for the metabotropic mGlu5 receptor over at least one of the metabotropic mGlu1 receptor, mGlu2 receptor and mGlu3 receptor, and preferably selective over all three thereof, are useful for the preparation of medicaments for the treatment of neuromuscular dysfunction of the lower urinary tract in mammals. A wide variety of suitable compds. is described. The medicament may contain the selective mGlu5 antagonist as the sole active agent, or may also contain one or more addnl. therapeutic agents for the treatment of neuromuscular dysfunction of the lower urinary tract in mammals. Also provided are methods of identifying selective mGlu5 antagonists that are useful for treating neuromuscular dysfunction of the lower urinary tract in mammals.

IT 329205-68-7
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (Selective mGlu5 antagonists for treatment of neuromuscular dysfunction of the lower urinary tract)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



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=> => d stat que 19
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L2      SEL PLU=ON L1 1- CHEM :          2 TERMS
L3      46 SEA FILE=HCAPLUS ABB=ON PLU=ON L2
L4      46 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR MTEP
L5      34433 SEA FILE=HCAPLUS ABB=ON PLU=ON ("OVERACTIVE BLADDER"/CV OR
      "BLADDER, DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7      148785 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR URINARY? OR ?CYSTITIS?
      OR URINE(2A)LEAK? OR ENURESIS OR BED(W)WETTING
L8      1 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND L7
L9      45 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 NOT L8
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L9 ANSWER 1 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:635588 HCAPLUS

TITLE: Antidepressant-like and anxiolytic-like actions of the mGlu5 receptor antagonist MTEP, microinjected into lateral septal nuclei of male Wistar rats

AUTHOR(S): Molina-Hernandez, Miguel; Tellez-Alcantara, Norma Patricia; Perez-Garcia, Julian; Olivera-Lopez, Jorge Ivan; Jaramillo, M. Teresa

CORPORATE SOURCE: Laboratorio de Psicobiología y Etología, Instituto de Investigaciones Psicológicas, Universidad Veracruzana, Jalapa, Veracruz, Mex.

SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2006), 30(6), 1129-1135
CODEN: PNPPD7; ISSN: 0278-5846

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study describes the effects of intra-lateral septal infusions of different doses of the mGluR5 antagonist MTEP in the DRL-72 s paradigm and the elevated plus-maze test in rats, two behavioral models known to be sensitive to antidepressant-like and anxiolytic-like drug effects, resp. Intra-lateral septal infusions of MTEP induced a dose-dependent (5.0 µg/µl, P < 0.05; 10.0 µg/µl, P < 0.05) increase in reinforced lever presses and a cohesive rightward shift of the inter-response time distribution (5.0 µg/µl, P < 0.05; 10.0 µg/µl, P < 0.05). These effects are indicative of antidepressant-like actions of the compound Desipramine, a prototypical antidepressant drug, induced (5.0 µg/µl; P < 0.05) similar effects. In the elevated plus-maze test, intra-lateral septal infusions of MTEP (5.0 µg/µl, P < 0.05; 10.0 µg/µl, P < 0.05) increased the exploration of the open arms without affecting locomotion. This anxiolytic-like effect was similar to that observed with the infusion of the benzodiazepine midazolam (10.0 µg/µl; P < 0.05) in the same brain area. It is concluded that intra-lateral septal infusions of the mGlu5 receptor antagonist MTEP produced antidepressant-like actions or anxiolytic-like effects in male rats.

L9 ANSWER 2 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:536861 HCPLUS

TITLE: mGlu1 and mGlu5 receptor antagonists lack anticonvulsant efficacy in rodent models of difficult-to-treat partial epilepsy

AUTHOR(S): Loescher, Wolfgang; Dekundy, Andrzej; Nagel, Jens; Danysz, Wojciech; Parsons, Chris G.; Potschka, Heidrun

CORPORATE SOURCE: Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine, Hannover, D-30559, Germany

SOURCE: Neuropharmacology (2006), 50(8), 1006-1015
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Modulation of metabotropic glutamate (mGlu) receptors represents an interesting new approach for the treatment of a range of neurological and psychiatric disorders. Several lines of evidence suggest that functional blockade of group I (mGlu1 and mGlu5) receptors may be beneficial for treatment of epileptic seizures. This study was conducted to investigate whether mGlu1 or mGlu5 receptor antagonists have the potential to block partial or secondarily generalized seizures as occurring in partial epilepsy, the most common and difficult-to-treat type of epilepsy in patients. For this purpose, we systemically administered novel highly

selective and brain penetrable group I mGlu receptor antagonists, i.e., the mGlu1 receptor antagonist EMQMCM [3-ethyl-2-methyl-quinolin-6-yl-(4-methoxy-cyclohexyl)-methanone methanesulfonate] and the mGlu5 receptor antagonist MTEP ([2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine), at doses appropriate for mGlu1 or mGlu5 receptor-mediated effects in rodent models of partial seizures. Two models were used: The 6-Hz electroshock model of partial seizures in mice and the amygdala-kindling model in rats. Clin. established antiepileptic drugs were included in the expts. for comparison. Antiepileptic drugs exerted significant anticonvulsant effects in both models, while EMQMCM and MTEP were ineffective in this regard, although both compds. were administered up to doses associated with essentially full receptor occupancy and with typical mGlu receptor-mediated effects in rodent models of anxiety or pain. Brain microdialysis for determining extracellular levels of MTEP following i.p. administration in rats substantiated that effective brain concns. were reached at times of our expts. in seizure models. The present results do not support a significant anticonvulsant potential of group I mGlu receptor antagonists in rodent models of difficult-to-treat partial epilepsy.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:314835 HCAPLUS

DOCUMENT NUMBER: 144:480888

TITLE: Neuroprotective potential of group I metabotropic glutamate receptor antagonists in two ischemic models

AUTHOR(S): Makarewicz, Dorota; Duszczak, Malgorzata; Gadamski, Roman; Danysz, Wojciech; Lazarewicz, Jerzy W.

CORPORATE SOURCE: Department of Neurochemistry, Medical Research Centre, Polish Academy of Sciences, Warsaw, 02-106, Pol.

SOURCE: Neurochemistry International (2006), 48(6-7), 485-490
CODEN: NEUIDS; ISSN: 0197-0186

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The neuroprotective potential of mGluR1 and mGluR5 antagonists (group I), EMQMCM and MTEP, resp. was studied using the 3 min forebrain ischemia model in Mongolian gerbils and the hypoxia-ischemia model in 7-day-old rats. Hypoxia-ischemia was induced by unilateral carotid occlusion followed by 75 min exposure to hypoxia (7.3% O₂ in N₂). Forebrain ischemia in gerbils was evoked by bilateral common carotid artery occlusion. The postischemic rectal body temperature in rat pups or

brain temperature of gerbils was measured. The drugs were administered i.p. three times every 2 h after the insult, each time in equal doses of 1.25, 2.5 or 5.0 mg/kg. After 2 wk brain damage was evaluated as weight decrease of the ipsilateral hemisphere in the rat pups or damage to CA1 pyramids in the gerbil hippocampus. The results demonstrated a dose dependent neuroprotection in both ischemic models by EMQMCM, while MTEP was neuroprotective only in the gerbil model of forebrain ischemia.

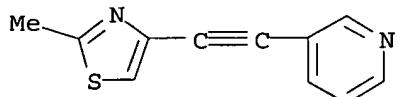
EMQMCM reduced postischemic hyperthermia in gerbils. Thus, the antagonists of mGluR1 and mGluR5 show differential neuroprotective ability in two models of brain ischemia. Postischemic hypothermia may be partially involved in the mechanism of neuroprotection following EMQMCM in gerbils.

IT 329205-68-7, MTEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

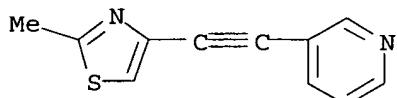
(neuroprotective potential of group I metabotropic glutamate receptor

antagonists in two ischemic models)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:314834 HCAPLUS
 TITLE: Antagonists of group I metabotropic glutamate receptors do not inhibit induction of ischemic tolerance in gerbil hippocampus
 AUTHOR(S): Duszczyk, Małgorzata; Gadamski, Roman; Ziembowicz, Apolonia; Lazarewicz, Jerzy W.
 CORPORATE SOURCE: Department of Neurochemistry, Medical Research Centre, Polish Academy of Sciences, Warsaw, 02-106, Pol.
 SOURCE: Neurochemistry International (2006), 48(6-7), 478-484
 CODEN: NEUIDS; ISSN: 0197-0186
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB In this study we tested the effect of antagonists of 2 subtypes of the group I metabotropic glutamate receptors (mGluRs GI) on the induction of ischemic tolerance in relation to brain temperature. These expts. were prompted by indications that glutamate receptors may participate in the mechanisms of ischemic preconditioning. The role of NMDA receptors in the induction of ischemic tolerance was debated while there is lack of information concerning the involvement of mGluRs GI in this phenomenon. The tolerance to injurious 3 min forebrain ischemia in Mongolian gerbils was induced 48 h earlier by 2 min preconditioning ischemia. Brain temperature was measured using telemetry equipment. EMQMCM and MTEP, antagonists of mGluR1 and mGluR5, resp., were injected i.p. at a dose of 5 mg/kg. They were administered either before preconditioning ischemia in a single dose or after 2 min ischemia three times every 2 h. Both antagonists did not inhibit the induction of ischemic tolerance. Thus, our data indicate that group I metabotropic glutamate receptors do not play an essential role in the induction of ischemic tolerance.
 IT INDEXING IN PROGRESS
 IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (group I metabotropic glutamate receptor antagonists do not inhibit induction of ischemic tolerance in gerbil hippocampus)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:287053 HCPLUS
 TITLE: Effects of group I metabotropic glutamate receptors blockade in experimental models of Parkinson's disease
 AUTHOR(S): Dekundy, Andrzej; Pietraszek, Małgorzata; Schaefer, Daniela; Cenci, M. Angela; Danysz, Wojciech
 CORPORATE SOURCE: Preclinical R&D, Merz Pharmaceuticals GmbH, Frankfurt am Main, 60318, Germany
 SOURCE: Brain Research Bulletin (2006), 69(3), 318-326
 CODEN: BRBUDU; ISSN: 0361-9230
 PUBLISHER: Elsevier Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The present study was devoted to investigate the effects of the metabotropic glutamate receptor (mGluR)5 antagonist [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) and the mGluR1 antagonist, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM), in animal studies indicative of antiparkinsonian-like activity such as haloperidol-induced catalepsy, hypoactivity in open field following haloperidol, and rotation in rats with unilateral 6-hydroxydopamine (OHDA)-induced lesions of the midbrain dopaminergic system (alone and in combination with -DOPA). Moreover, antidyskinetic activity of different mGluR ligands was evaluated in the rat model of -DOPA-induced dyskinesia. Both MTEP (5 mg/kg) and EMQMCM (4 mg/kg) slightly inhibited haloperidol (0.5 mg/kg)-induced catalepsy. However, neither substance reversed the hypoactivity produced by haloperidol (0.2 mg/kg). Although MTEP did not produce significant turning, it inhibited contralateral rotations after -DOPA (at 5 mg/kg) and alleviated -DOPA-induced dyskinesia (at 2.5 and 5 mg/kg) in 6-OHDA-lesioned rats. In contrast, mGluR1 antagonists EMQMCM and RS-1-aminoindan-1,5-dicarboxylic acid (AIDA) failed to modify -DOPA-induced dyskinesia. The results of the present study suggest that either subtype of group I of mGluRs may be involved in the pathol. altered circuitry in the basal ganglia. However, the equivocal results do not strongly support the hypothesis that mGluR1 and mGluR5 antagonists may be beneficial in the symptomatic treatment of Parkinson's disease. However, mGluR5 antagonists may prove useful for the symptomatic treatment of -DOPA-induced dyskinesia.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:171402 HCPLUS
 DOCUMENT NUMBER: 144:363335
 TITLE: Functional interaction of NMDA and group I metabotropic glutamate receptors in negatively reinforced learning in rats
 AUTHOR(S): Gravius, A.; Pietraszek, M.; Schmidt, W. J.; Danysz, W.
 CORPORATE SOURCE: Preclinical R&D, Merz Pharmaceuticals, Frankfurt am Main, 60318, Germany
 SOURCE: Psychopharmacology (Berlin, Germany) (2006), 185(1), 58-65
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Rationale: The role of glutamatergic system in learning and memory has been extensively studied, and especially N-methyl-d-aspartate (NMDA) receptors have been implicated in different learning and memory processes. Less is known, however, about group I metabotropic glutamate (mGlu) receptors in this field. Recent studies indicated that the coactivation of both NMDA and group I mGlu receptors is required for the induction of long-term potentiation (LTP) and learning. Objective: The purpose of the study is to evaluate if there is a functional interaction between NMDA and group I mGlu receptors in two different models of aversive learning. Methods: Effects of NMDA, mGlu₁, and mGlu₅ receptor antagonists on acquisition were tested after systemic coadministration of selected ineffective doses in passive avoidance (PA) and fear-potentiated startle (FPS). Results: Interaction in aversive learning was investigated using selective antagonists: (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) for mGlu₁, [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) for mGlu₅, and (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate [(+)-MK-801] for NMDA receptors. In PA, the coapplication of MTEP at a dose of 5 mg/kg and (+)-MK-801 at a dose of 0.1 mg/kg 30 min before training impaired the acquisition tested 24 h later. Similarly, EMQMCM (2.5 mg/kg) plus (+)-MK-801 (0.1 mg/kg), given during the acquisition phase, blocked the acquisition of the PA response. In contrast, neither the combination of MTEP (1.25 mg/kg) nor EMQMCM (5 mg/kg) plus (+)-MK-801 (0.05 mg/kg) was effective on the acquisition assessed in the FPS paradigm. Conclusion: The findings suggest differences in the interaction of the NMDA and mGlu group I receptor types in aversive instrumental conditioning vs. conditioning to a discrete light cue.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:139299 HCPLUS
 DOCUMENT NUMBER: 144:360901
 TITLE: Thermodynamic description of heat and spin transport in magnetic nanostructures
 AUTHOR(S): Gravier, Laurent; Serrano-Guisan, Santiago; Reuse, Francois; Ansermet, Jean-Philippe
 CORPORATE SOURCE: Institut de Physique des Nanostructures, Ecole Polytechnique Federale de Lausanne, Lausanne-EPFL, CH-1015, Switz.
 SOURCE: Physical Review B: Condensed Matter and Materials Physics (2006), 73(2), 024419/1-024419/11
 CODEN: PRBMDO; ISSN: 1098-0121
 PUBLISHER: American Physical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Spin-dependent heat and charge transport perpendicular to the plane of magnetic Co/Cu multilayers was studied exptl. and interpreted in the framework of the thermodn. of irreversible processes. The thermogalvanic voltage(TGV) is introduced. It measures the ac voltage response to a small temperature oscillation while a dc current is driven through the sample. TGV presents a magnetic response (MTGV) of 50%, much larger than magnetoresistance (GMR) and the magneto-thermoelec. power (MTEP). The linear equations for transport of heat, charge, and spin-polarized currents in magnetic and nonmagnetic mediums are applied to a multilayer structure. The role of spin mixing in GMR, MTEP, and MTGV is shown. In particular, the asymmetry of the spin-mixing gives rise to spin-dependent effective Peltier coeffs. The three measurements can be accounted for with two parameters expressing the spin dependence of the transport coeffs.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:104060 HCPLUS
 DOCUMENT NUMBER: 144:331314
 TITLE: Synthesis of 4-arylethynyl-2-methyloxazole derivatives as mGluR5 antagonists for use in the treatment of drug abuse
 AUTHOR(S): Iso, Yasuyoshi; Kozikowski, Alan P.
 CORPORATE SOURCE: Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL, 60612, USA
 SOURCE: Synthesis (2006), (2), 243-246
 CODEN: SYNTBF; ISSN: 0039-7881
 PUBLISHER: Georg Thieme Verlag
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB In structure-activity relationship studies directed toward the use of mGluR5 antagonists in the treatment of drug abuse, a convenient means for gaining access to the oxazole analogs of MTEP was sought. Toward this end, the aldehyde group in 2-methyloxazole-4-carboxaldehyde was successfully converted to a trimethylsilylethynyl group via the preparation of a dibromo olefin, conversion to acetylide using NaHMDS and MeLi, and trapping with TMSCl. The resulting versatile intermediate, 2-methyl-4-[(trimethylsilyl)ethynyl]oxazole, was subjected to a modified Sonogashira coupling reaction involving an in situ desilylation reaction with Bu4NF and palladium-catalyzed coupling with an aryl or heteroaryl iodide to give the desired oxazole analogs.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:20956 HCPLUS
 DOCUMENT NUMBER: 144:274179
 TITLE: Synthesis and Structure-Activity Relationships of 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine Analogues as Potent, Noncompetitive Metabotropic Glutamate Receptor Subtype 5 Antagonists; Search for Cocaine Medications
 AUTHOR(S): Iso, Yasuyoshi; Grajkowska, Ewa; Wroblewski, Jarda T.; Davis, Jared; Goeders, Nicholas E.; Johnson, Kenneth M.; Sanker, Subramaniam; Roth, Bryan L.; Tueckmantel, Werner; Kozikowski, Alan P.
 CORPORATE SOURCE: Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL, 60612, USA
 SOURCE: Journal of Medicinal Chemistry (2006), 49(3), 1080-1100
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Recent genetic and pharmacol. studies have suggested that the metabotropic glutamate receptor subtype 5 (mGluR5) may represent a druggable target in identifying new therapeutics for the treatment of various central nervous system disorders including drug abuse. In particular, considerable attention in the mGluR5 field has been devoted to identifying ligands that bind to the allosteric modulatory site, distinct from the site for the primary agonist glutamate. Both 2-methyl-6-(phenylethynyl)pyridine (MPEP)

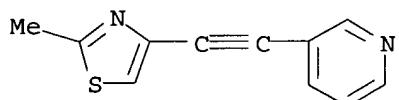
and its analog 3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (MTEP) have been shown to be selective and potent noncompetitive antagonists of mGluR5. Because of results presented in this study showing that MTEP prevents the reinstatement of cocaine self-administration caused by the presentation of environmental cues previously associated with cocaine availability, a series of analogs of MTEP was prepared with the aim of gaining a better understanding of the structural features relevant to its antagonist potency and with the ultimate aim of investigating the effects of such compds. in blunting the self-administration of cocaine. These efforts have led to the identification of compds. showing higher potency as mGluR5 antagonists than either MPEP or MTEP. Two compds. exhibited functional activity as mGluR5 antagonists that are 490 and 230 times, resp., better than that of MTEP.

IT 329205-68-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of methyl[(pyridinyl)ethynyl]thiazole derivs. and study of their activity as noncompetitive metabotropic glutamate receptor subtype-5 (mGluR5) antagonists)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1338537 HCAPLUS

DOCUMENT NUMBER: 144:462438

TITLE: N-methyl-D-aspartate and group I metabotropic glutamate receptors are involved in the expression of ethanol-induced sensitization in mice

AUTHOR(S): Kotlinska, Jolanta; Bochenski, Marcin; Danysz, Wojciech

CORPORATE SOURCE: Department of Pharmacology and Pharmacodynamics, Medical University, Lublin, 20-081, Pol.

SOURCE: Behavioural Pharmacology (2005), Volume Date 2006, 17(1), 1-8

CODEN: BPHEL; ISSN: 0955-8810

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of Acamprosate and ionotropic uncompetitive N-methyl-D-aspartate receptor antagonists and group I metabotropic glutamatergic receptor antagonists on the expression of ethanol-induced sensitization were investigated in mice. The results indicated that Acamprosate (200 and 400 mg/kg) and N-methyl-D-aspartate receptor antagonists, Neramexane (10 and 20 mg/kg) and MK-801 (0.1 and 0.2 mg/kg), inhibited the expression of ethanol-induced sensitization. Acamprosate, but not the other compds. tested, also blocked the stimulant effect of acute injections of ethanol. Among the group I metabotropic glutamatergic receptor antagonists, only the metabotropic glutamatergic receptor 5 antagonist, MTEP (5, 10, and 20 mg/kg), showed an effect similar

to the N-methyl-D-aspartate receptor antagonists. The metabotropic glutamatergic receptor 1 antagonist, EMQMCM (5, 10, and 20 mg/kg), however, potentiated the inhibitory effect of MK-801 on the expression of ethanol-induced sensitization. The findings indicate that glutamatergic neurotransmission is important in the ethanol-induced sensitization process, and suggest that co-administration of metabotropic glutamatergic receptor 1 antagonists and N-methyl-D-aspartate receptor antagonists may be useful in therapy for alcoholism.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1277087 HCAPLUS

DOCUMENT NUMBER: 144:120871

TITLE: In vitro metabolic studies on the selective metabotropic glutamate receptor sub-type 5 (mGluR5) antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP)

AUTHOR(S): Green, Mitchell D.; Yang, Xiaoqing; Cramer, Merryl; King, Christopher D.

CORPORATE SOURCE: Medicinal Chemistry, DMPK, Merck Research Laboratories San Diego, San Diego, CA, 92121, USA

SOURCE: Neuroscience Letters (2006), 391(3), 91-95
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Metabotropic glutamate receptors (mGluR) are G-protein-coupled receptors that play a major role in modulatory pathways in the CNS and have been suggested to have pharmacol. implications in pain, psychiatric disorders and other neurol. states. 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) is a specific and selective antagonist for the mGluR sub-type 5. Previous studies using rat liver microsomes showed that the major oxidative metabolites of MTEP are a hydroxymethyl metabolite (M1), two oxides (M2 and M4), a thiazole-ring opened metabolite (M3) and CO₂ (M5). In the present study, the authors examined the metabolism

of

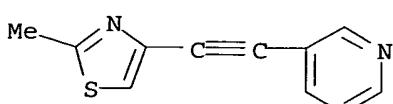
MTEP in liver microsomes and expressed rat and human CYP isoforms. In rat liver microsomes, metabolic stability studies accurately predicted the in vivo clearance for MTEP. Incubation of MTEP with expressed rat and human CYP isoforms showed that CYP1A and CYP2C isoforms are primarily responsible for the metabolism of this compound. The results suggest that species differences in MTEP metabolism is possible and could contribute to specie-differences in biol. effects of the compound

IT 329205-68-7D, MTEP, metabolites

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro metabolism of selective metabotropic glutamate receptor sub-type 5 (mGluR5) antagonist MTEP)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)

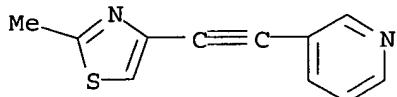


IT 329205-68-7, MTEP

RL: PKT (Pharmacokinetics); BIOL (Biological study)
 (in vitro metabolism of selective metabotropic glutamate receptor sub-type
 5 (mGluR5) antagonist MTEP)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1205641 HCAPLUS

DOCUMENT NUMBER: 144:205101

TITLE: In vitro microsomal metabolic studies on a selective mGluR5 antagonist MTEP: Characterization of in vitro metabolites and identification of a novel thiazole ring opening aldehyde metabolite

AUTHOR(S): Yang, X.; Chen, W.

CORPORATE SOURCE: Drug Metabolism and Pharmacokinetics Group, Department of Medicinal Chemistry, Merck Research Laboratories, San Diego, CA, USA

SOURCE: Xenobiotica (2005), 35(8), 797-809

CODEN: XENOHB; ISSN: 0049-8254

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In vitro liver microsomal studies revealed that [14C] MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl] pyridine) was metabolized into three major oxidative metabolites. Metabolite 1 (M1) was shown to be a hydroxymethyl metabolite; M2 was shown to be a pyridine oxide. Moreover, a novel aldehyde metabolite (M3) was identified from mouse liver microsomes. The structure of the aldehyde M3 was elucidated by LC/MS/MS. In addition, methoxyamine, an aldehyde-trapping agent, and accurate mass measurement using a high-resolution quadrupole-time of flight (Q-TOF) instrument, were used to confirm the proposed thiazole ring-opening structure of M3. A mechanism for aldehyde M3 formation was postulated based on MTEP incubation studies with 18O₂ and H₂ 18O using mouse liver microsomes. MTEP was initially oxidized at sulfur, followed by subsequent C4-C5 of thiazole epoxidn., thiozole ring opening and further oxidative desulfation. This proposed thiazole ring-opening mechanism might represent a novel metabolism pathway for xenobiotics containing a thiazole moiety. Species differences in the metabolism of MTEP were observed in mouse, rat, dog, monkey and human liver microsomes. Mouse appears to generate all three oxidative metabolites to a greater extent than other species examined

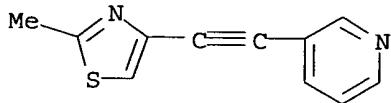
IT 329205-68-7, MTEP

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(in vitro microsomal metabolic studies on mGluR5 antagonist MTEP and its metabolites)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1182395 HCAPLUS

DOCUMENT NUMBER: 144:65371

TITLE: The metabotropic glutamate 5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine reduces ethanol self-administration in multiple strains of alcohol-preferring rats and regulates olfactory glutamatergic systems

AUTHOR(S): Cowen, Michael S.; Djouma, Elvan; Lawrence, Andrew J.

CORPORATE SOURCE: Howard Florey Institute, University of Melbourne, Victoria, Australia

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 315(2), 590-600

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

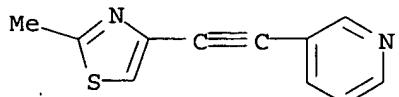
AB The metabotropic glutamate 5 receptor (mGlu5) receptor has been implicated as having a role in pain modulation, anxiety, and depression, as well as drug-seeking behavior. In the present study, we examined the effect of the selective mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) on operant ethanol self-administration by two strains of rats, the Fawn-Hooded (FH) rat and the inbred alc.-preferring (iP) rat. MTEP (2 mg/kg i.p.) caused a significant reduction in responding for ethanol by both strains of rats; however, in the iP rats, MTEP also induced apparent sedation at this dose, although still reduced alc. responding at lower doses. Chronic MTEP (2 mg/kg/day) caused a significant reduction in ethanol consumption by FH rats in a two-bottle preference test; however, chronic treatment with this dose had no effect on anxiety-like behavior or depressive-like behavior in FH rats, suggesting the dose used was subthreshold for anxiolytic or antidepressive-like effects. Finally, repeated dosing with MTEP (2 mg/kg i.p.) caused significant redns. in expression of the mRNA encoding the NR1 subunit of the N-methyl-D-aspartate receptor and the GluR2 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor in the cingulate cortex. A significant decrease in NR1 expression also occurred in the piriform cortex. Chronic MTEP also caused a significant decrease in mGlu5 gene expression and a significant increase in dopamine transporter and dopamine D2-like receptor binding within the olfactory tubercle. Collectively, these data suggest that MTEP can reduce alc.-seeking behavior in different rodent models of alcoholism, and this effect is associated with regulation of cortical glutamate systems, particularly those in olfactory-related regions.

IT 329205-68-7, MTEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(metabotropic glutamate 5 receptor antagonist MTEP reduces ethanol self-administration in multiple strains of alc.-preferring rats

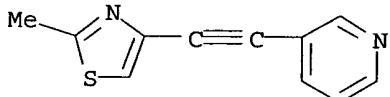
and regulates olfactory glutamatergic systems)
RN 329205-68-7 HCAPLUS
CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1091076 HCAPLUS
DOCUMENT NUMBER: 144:121431
TITLE: Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands
AUTHOR(S): Frisby, Claudine L.; Mattsson, Jan P.; Jensen, Joergen M.; Lehmann, Anders; Dent, John; Blackshaw, L. Ashley
CORPORATE SOURCE: Nerve-Gut Research Laboratory, Royal Adelaide Hospital, Adelaide, Australia
SOURCE: Gastroenterology (2005), 129(3), 995-1004
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated by metabotropic glutamate receptors (mGluRs). Group I mGluRs (mGluR1 and 5) have excitatory effects on neurons, whereas group II (mGluR2 and 3) and group III (mGluR4, 6, 7, and 8) are inhibitory. This study determined the effect of mGluRs on triggering of TLESR and reflux in an established conscious ferret model. Methods: Esophageal manometric/pH studies were performed in ferrets with chronic esophagostomies. TLESR were induced by a gastric load of 25 mL glucose (pH 3.5) and 30 mL air. Results: In control treated animals, gastric load induced 3.52 ± 0.46 TLESRs per 47-min study, 89.7% of which were associated with reflux episodes ($n = 16$). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal $71\% \pm 7\%$ inhibition at $35 \mu\text{mol}/\text{kg}$ ($n = 9$; $P < .0001$). MPEP also significantly reduced reflux episodes ($P < .001$) and increased basal lower esophageal sphincter pressure ($P < .05$). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analog, MTEP, had more potent effects ($90\% \pm 6\%$ inhibition TLESR at $40 \mu\text{mol}/\text{kg}$; $n = 8$; $P < .0001$). In contrast, the group I agonist DHPG tended to increase TLESR. The group II agonist (2R, 4R)-APDC was ineffective, whereas the group III agonist L-AP4 slightly reduced TLESR ($33\% \pm 11 \mu\text{mol}/\text{kg}$; $P < .05$). The selective mGluR5 agonist (S)-3, 4-DCPG inhibited TLESR by 54% at $15 \mu\text{mol}/\text{kg}$ ($P < .01$). Conclusions: mGluR5 antagonists potently inhibit TLESR and reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. MGLuR5 antagonists are therefore promising as therapy for patients with GERD.
IT 329205-68-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor inhibitor 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine inhibited TLESR and swallowing, reduced reflux

episode and increased basal lower esophageal sphincter pressure in ferret with chronic esophagostomies)
RN 329205-68-7 HCAPLUS
CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)

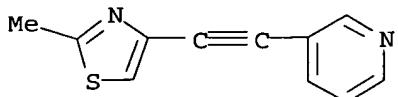


REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:861882 HCAPLUS
DOCUMENT NUMBER: 143:298928
TITLE: Potential antidepressant-like effect of MTEP , a potent and highly selective mGluR5 antagonist
AUTHOR(S): Palucha, Agnieszka; Branski, Piotr; Szewczyk, Bernadeta; Wieronska, Joanna M.; Klak, Kinga; Pilc, Andrzej
CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31-343, Pol.
SOURCE: Pharmacology, Biochemistry and Behavior (2005), 81(4), 901-906
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The involvement of glutamate in the pathophysiol. of depression has been suggested by a number of expts. It was well established that compds., which decreased glutamatergic transmission via blockade of NMDA receptor, produced antidepressant-like action in animal tests and models. The present study was carried out to investigate whether a selective mGluR5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) induces antidepressant-like effects after i.p. injections in male Wistar rats or male C57BL/6J mice. Potential antidepressant-like activity of MTEP was evaluated using the forced swimming test (FST) in rats, the tail suspension test (TST) in mice and the olfactory bulbectomy (OB) model of depression in rats. The results of our studies showed, that MTEP (0.3-3 mg/kg) produced a significant dose-dependent decrease in the immobility time of mice in the TST, however, at doses of 1 or 10 mg/kg, it did not influence the behavior of rats in the FST in rats. Moreover, the repeated administration of MTEP (1 mg/kg) attenuated the OB-related hyperactivity of rats in the open field test, in the manner similar to that seen following chronic (but not acute) treatment with typical antidepressant drugs. These data suggest that MTEP, which is considered to be a potential therapeutic agent, may play a role in the therapy of depression.

IT 329205-68-7, MTEP
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potential antidepressant-like effect of MTEP, potent and highly selective mGluR5 antagonist)

RN 329205-68-7 HCAPLUS
CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:844852 HCPLUS

DOCUMENT NUMBER: 143:279142

TITLE: MTEP, a new selective antagonist of the metabotropic glutamate receptor subtype 5 (mGluR5), produces antiparkinsonian-like effects in rats

AUTHOR(S): Ossowska, K.; Konieczny, J.; Wolfarth, S.; Pilc, A.

CORPORATE SOURCE: Department of Neuro-Psychopharmacology, Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31-343, Pol.

SOURCE: Neuropharmacology (2005), 49(4), 447-455

CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of the present study was to examine a potential antiparkinsonian-like action of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), a new non-competitive antagonist of mGluR5, in the rat models. This compound has affinity for mGluR5 in a nanomolar concentration range and seems to be superior to the earlier known antagonists in terms of its specificity and bioavailability. Catalepsy and muscle rigidity induced by haloperidol administered at doses of 0.5 and 1 mg/kg were regarded as models of parkinsonian akinesia and muscle rigidity, resp. MTEP at doses between 0.5 and 3 mg/kg i.p. decreased the haloperidol-induced muscle rigidity measured as an increased muscle resistance of the rat's hind leg in response to passive extension and flexion at the ankle joint. The strongest and the longest effect was observed after the dose of 1 mg/kg. MTEP (0.5-3 mg/kg i.p.) also reduced the haloperidol-induced increase in electromyog. (EMG) activity recorded in the gastrocnemius and tibialis anterior muscles. MTEP (3 and 5 mg/kg i.p.) inhibited the catalepsy induced by haloperidol. The present study confirms earlier suggestions that the antagonists of mGluR5 may possess antiparkinsonian properties. However, selective mGluR5 antagonists may be more effective in inhibiting parkinsonian muscle rigidity than parkinsonian akinesia.

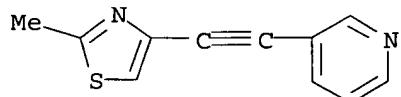
IT 329205-68-7, MTEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mGluR5 antagonist MTEP produces antiparkinsonian-like effects in rats)

RN 329205-68-7 HCPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS

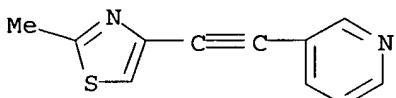
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:739564 HCPLUS
 TITLE: Synthesis of an easily 18F-labeled and high affinity candidate radioligand for PET imaging of brain mGluR5 receptors
 AUTHOR(S): Simeon, Fabrice G.; Patterson, Velvet M.; Chin, Frederick T.; Innis, Robert B.; Pike, Victor W.
 CORPORATE SOURCE: Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, 20892, USA
 SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-049. American Chemical Society: Washington, D. C.
 CODEN: 69HFCL
 DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
 LANGUAGE: English
 AB MTEP (1) has provided a lead for some promising radioligands for imaging human brain mGluR5 receptors with positron emission tomog. (PET) in vivo. Easily 18F-labeled ligands are still however sought for this purpose. We have developed a strategy for labeling in a fluoromethyl group at the 2-position of the 1,3-thiazole ring. Target fluoro compound (2) was prepared in 3 steps via 4-(trimethylsilyl-ethynyl)-2-fluoromethyl-1,3-thiazole (TFT) and bromo analog (3) in 8 steps. 2 was found to have an IC50 of 26 pM. Treatment of 3 with 1,18F3;fluoride ion gave 1,18F3;2 in high radiochem. yield under mild conditions (MeCN, 800C, 20 min) for evaluation as a PET radioligand. Labeling at the 2-position of the 1,3-thiazole ring opens up the possibility to explore multiple variations in the substitution pattern of the Ph ring in a search for effective PET radioligands. TFT may serve as a key synthon for the generic syntheses of many such ligands.

L9 ANSWER 18 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:580046 HCPLUS
 DOCUMENT NUMBER: 143:260117
 TITLE: mGluR5, but not mGluR1, antagonist modifies MK-801-induced locomotor activity and deficit of prepulse inhibition
 AUTHOR(S): Pietraszek, M.; Gravius, A.; Schaefer, D.; Weil, T.; Trifanova, D.; Danysz, W.
 CORPORATE SOURCE: Preclinical R&D, Merz Pharmaceuticals, Frankfurt am Main, 60318, Germany
 SOURCE: Neuropharmacology (2005), 49(1), 73-85
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Hypoglutamatergic theory of schizophrenia is substantiated by observation that high affinity uncompetitive antagonists of NMDA receptors such as PCP can induce psychotic symptoms in humans. Recently, metabotropic glutamate receptors of the mGluR5 type have also been discussed as possible players in this disease. However, less is known about the potential contribution of mGluR1 in schizophrenia. Therefore, the aim of the present study was to compare the effect of selective mGluR1 antagonist EMQMCM, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate and mGluR5 antagonist MTEP ((2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine) either alone or in combination with (+)MK-801 in a prepulse inhibition (PPI) model and locomotor activity

tests. Addnl., the effect of both mGluR1 and mGluR5 antagonists on (+)MK-801-evoked ataxia was tested. In contrast to (+)MK-801, which induced disruption of PPI, neither MTEP (1.25-5 mg/kg) nor EMQMCM (0.5-4 mg/kg) altered the PPI. However, MTEP, but not EMQMCM, enhanced disruption of PPI induced by (+)MK-801. Although neither mGluR1 nor mGluR5 antagonists given alone changed locomotor activity of rats, MTEP at 5 mg/kg potentiated the effect of (+)MK-801 while EMQMCM (up to 4 mg/kg) turned out to be ineffective. On the other hand, EMQMCM, but not MTEP, enhanced ataxia evoked by MK-801. The present results demonstrate that blockade of mGluR1 and mGluR5 evokes different effects on behavior induced by NMDA receptor antagonists.

IT 329205-68-7, MTEP
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (mGluR5, but not mGluR1, antagonist modifies MK-801-induced locomotor activity and deficit of prepulse inhibition)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)

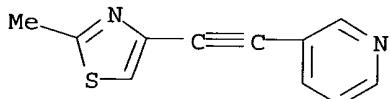


REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:511877 HCAPLUS
 DOCUMENT NUMBER: 143:126567
 TITLE: Neuroprotective activity of the mGluR5 antagonists MPEP and MTEP against acute excitotoxicity differs and does not reflect actions at mGluR5 receptors
 AUTHOR(S): Lea, Paul M.; Movsesyan, Vilen A.; Faden, Alan I.
 CORPORATE SOURCE: Department of Neuroscience, Georgetown University Medical Center, Washington, DC, USA
 SOURCE: British Journal of Pharmacology (2005), 145(4), 527-534
 CODEN: BJPCBM; ISSN: 0007-1188
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Neuroprotection has been reported after either activation or blockade of the group I metabotropic glutamate receptor subtype 5 (mGluR5). However, some recent evidence suggests that protection provided by mGluR5 antagonists may reflect their ability to inhibit N-methyl-D-aspartate (NMDA) receptor activity. Here, in both rat and mouse cortical neurons, we compare the neuroprotective actions of two mGluR5 antagonists: 2-methyl-6-(phenylethynyl)-pyridine (MPEP), which has been commonly used and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), a more recently developed compound believed to have greater mGluR5 selectivity. We have previously shown that MPEP directly reduces single-channel NMDA receptor open time at the same concns. (20 μM or greater) that show neuroprotection, whereas MPEP antagonizes mGluR5 agonist ((RS)-2-chloro-5-hydroxyphenylglycine (CHPG))-induced changes in inositol phosphates (IP) at concns. as low as 0.2 μM. In the present studies, MTEP significantly inhibited CHPG-mediated IP

hydrolysis at concns. as low as 0.02 μ M. In contrast to MPEP, which significantly reduced glutamate- or NMDA-mediated cell death in primary rat neuronal cultures at a concentration of 20 μ M, small neuroprotective effects were observed with MTEP only at a concentration of 200 μ M. Neither MPEP- nor MTEP-mediated mGluR5 inhibition had any effect on etoposide-induced apoptotic cell death. In rat cortical neurons, the neuroprotective effects of MTEP at very high concns., like those of MPEP, reflect ability to directly reduce NMDA receptor peak and steady-state currents. We also compared the effects of MPEP and MTEP in primary cortical neuronal cultures from parental and mGluR5 knockout mice. Both agents were neuroprotective, at high concns. in normal as well as in the knockout cultures. In contrast to rat cortical neurons, neither MPEP nor MTEP appears to directly alter NMDA receptor activity. Combined, these studies support the conclusion that MTEP has greater mGluR5 selectivity than MPEP, and that neuroprotection provided by either antagonist in neuronal cultures does not reflect inhibition of mGluR5 receptors.

IT 329205-68-7, MTEP
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (neuroprotective activity of mGluR5 antagonists MPEP and MTEP against acute excitotoxicity differs and does involve mGluR5 receptors)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl] - (9CI) (CA INDEX NAME)

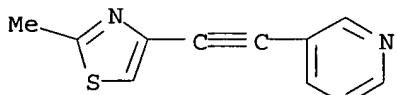


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:412797 HCAPLUS
 DOCUMENT NUMBER: 143:19835
 TITLE: Selective mGlu5 receptor antagonist MTEP attenuates naloxone-induced morphine withdrawal symptoms
 AUTHOR(S): Palucha, Agnieszka; Branski, Piotr; Pilc, Andrzej
 CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Krakow, PL 31-343, Pol.
 SOURCE: Polish Journal of Pharmacology (2004), 56(6), 863-866
 CODEN: PJPAE3; ISSN: 1230-6002
 PUBLISHER: Polish Academy of Sciences, Institute of Pharmacology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Several lines of evidence suggest a crucial involvement of glutamate in the mechanism of drug addiction. The involvement of group I mGlu receptors in the mechanism of addiction has also been proposed. Given the recent discovery of selective and brain penetrable mGlu5 receptor antagonists, the effects of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) were evaluated in the naloxone-precipitated morphine withdrawal model. Expts. were performed on male C57BL/6J (20-25 g) mice. Mice were rendered morphine-dependent and withdrawal was precipitated with naloxone. Two hours and 15 min after the last dose of morphine, mice were injected with a mGlu5 receptor antagonist. MTEP (1-10 mg/kg) in a dose-dependent manner inhibited the naloxone-induced symptoms of

morphine withdrawal in morphine-dependent mice, remaining without any effect on the locomotor activity of mice. The data suggest that selective mGlu5 receptor antagonists may play a role in the therapy of drug-dependence states.

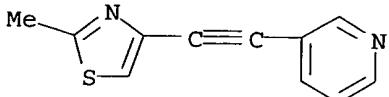
IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (selective mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine dose-dependently attenuated naloxone-induced symptoms of morphine withdrawal symptoms without locomotor activity in morphine-dependent mouse model)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:387247 HCAPLUS
 DOCUMENT NUMBER: 143:1087
 TITLE: Anxiolytic-like effects of mGlu1 and mGlu5 receptor antagonists in rats
 AUTHOR(S): Pietraszek, Małgorzata; Sukhanov, Ilia; Maciejak, Piotr; Szyndler, Janusz; Gravius, Andreas; Wisłowska, Aleksandra; Plaznik, Adam; Bespalov, Anton Y.; Danysz, Wojciech
 CORPORATE SOURCE: Preclinical R&D, Merz Pharmaceuticals GmbH, Frankfurt am Main, 60318, Germany
 SOURCE: European Journal of Pharmacology (2005), 514(1), 25-34
 CODEN: EJPHAZ; ISSN: 0014-2999
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The purpose of the present study was to compare anxiolytic activity of the metabotropic glutamate receptor 1 (mGlu) antagonist, EMQMCM ((3-ethyl-2-methyl-quinolin-6-yl)- (4-methoxy-cyclohexyl)-methanone methanesulfonate) and the mGlu5 receptor antagonist MTEP ((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine) and MPEP (2-methyl-6-(phenylethynyl)pyridine) in animal models of anxiety. In the elevated plus maze, diazepam (1 mg/kg), but not the mGlu1 or mGlu5 receptor antagonists induced anxiolytic-like effects. Meanwhile, MTEP (2.5 and 5 mg/kg), EMQMCM (5 mg/kg), and diazepam (2 mg/kg) all significantly inhibited fear potentiated startle. In the contextual fear conditioning test, MTEP (1.25 and 2.5 but not 5 mg/kg) and EMQMCM (0.6 to 5 mg/kg) attenuated freezing responding. In the Geller-Seifter conflict test, MPEP (1 and 3 mg/kg), MTEP (3 mg/kg), chlordiazepoxide (10 and 20 mg/kg) and midazolam (1 mg/kg) all facilitated punished responding, while EMQMCM failed to produce any significant effects up to 3 mg/kg dose. To summarize, the present data further support a significant anxiolytic potential of group I mGlu receptor antagonists, while suggesting the effects of mGlu1 receptor antagonists may depend on the exptl. procedure and may be qual. different from those of mGlu5 receptor antagonists.

IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (anxiolytic-like effects of mGlu1 and mGlu5 receptor antagonists in
 rats)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

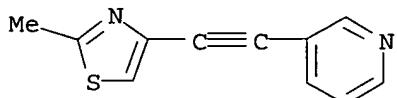
L9 ANSWER 22 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:330449 HCAPLUS
 DOCUMENT NUMBER: 142:368062
 TITLE: Metabotropic glutamate receptor mGlu5 is a mediator of appetite and energy balance in rats and mice
 Bradbury, Margaret J.; Campbell, Una; Giracello, Darlene; Chapman, Deborah; King, Chris; Tehrani, Lida; Cosford, Nicholas D. P.; Anderson, Jeff; Varney, Mark A.; Strack, Alison M.
 CORPORATE SOURCE: Department of Neuropharmacology, Merck Research Laboratories, San Diego, CA, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 313(1), 395-402
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The metabotropic glutamate receptor subtype mGlu5 modulates central reward pathways. Many transmitter systems within reward pathways affect feeding. We examined the potential role of mGlu5 in body weight regulation using genetic and pharmacol. approaches. Adult mice lacking mGlu5, mGluR5-/-, weighed significantly less than littermate controls (mGluR5+/+), despite no difference in ad libitum food intake. After overnight food deprivation, mGluR5-/- mice ate significantly less than their mGluR5+/+ controls when refeeding. When on a high fat diet, mGluR5-/- mice weighed less and had decreased plasma insulin and leptin concns. The selective mGlu5 antagonist MTEP [3-[(2-methyl-1,3-thiazol-4-yl)-ethynyl]-pyridine; 15 mg/kg s.c.] reduced refeeding after overnight food deprivation in mGluR5+/+, but not mGluR5-/- mice, demonstrating that feeding suppression is mediated via a mGlu5 mechanism. MTEP (1-10 mg/kg) decreased night-time food intake in rats in a dose-related manner. At 10 mg/kg, MTEP injected at 8.5, 4.5, or 0.5 h before refeeding reduced overnight food intake by approx. .apprx.30%. Diet-induced obese (DIO) and age-matched lean rats were treated for 12 days with MTEP (3 or 10 mg/kg/day s.c.), dextroamphetamine (3 mg/kg/day s.c.), or vehicle. Daily and cumulative food intakes were reduced in DIO rats by MTEP and dextroamphetamine. Weight gain was prevented with MTEP (3 mg/kg), and weight and adiposity loss was seen with MTEP (10 mg/kg) and dextroamphetamine. Caloric efficiency was decreased, suggesting increased energy expenditure. In lean rats, similar, although smaller, effects were observed. In conclusion,

using genetic and pharmacol. approaches, we have shown that mGlu5 modulates food intake and energy balance in rodents.

IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); BIOL (Biological study)
 (metabotropic glutamate receptor mGlu5 as mediator of appetite and energy balance in rats and mice)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

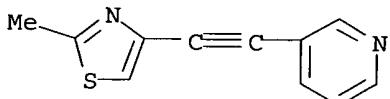
L9 ANSWER 23 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:309176 HCAPLUS
 DOCUMENT NUMBER: 142:456886
 TITLE: Blockade of the mGlu5 receptor decreases basal and stress-induced cortical norepinephrine in rodents
 AUTHOR(S): Page, Michelle E.; Szeliga, Paul; Gasparini, Fabrizio; Cryan, John F.
 CORPORATE SOURCE: Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA, 19129, USA
 SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 240-246
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Glutamate, the major excitatory neurotransmitter in the brain mediates its effects by both ionotropic and metabotropic receptor subtypes. Recently, the search for selective ligands for glutamate receptor subtypes has led to the discovery of 2-methyl-6-(phenylethynyl)pyridine (MPEP), an antagonist specific for metabotropic glutamate receptor 5 (mGlu5). This receptor is highly expressed in limbic forebrain regions and is thought to modulate anxiety-related processes. The noradrenergic nucleus locus caeruleus (LC) is an important mediator of stress responses and dysfunction of this system is implicated in affective disorders such as anxiety and depression. The authors sought to assess the effects of mGlu5 receptor antagonists, MPEP and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) on cortical norepinephrine (NE) levels. In vivo microdialysis and high-pressure liquid chromatog. with electrochem. detection (HPLC-ED) were used to assess the effects of mGlu5 antagonism on extracellular NE in the frontal cortex, a major terminal field of the LC. Blockade of the mGlu5 receptor elicited significant redns. in extracellular NE in the frontal cortex. The benzodiazepine diazepam also reduced cortical NE. Furthermore, MPEP administration attenuated stress-induced increases in extracellular NE. Taken together, these data show that MPEP and MTEP, through their blockade of the mGlu5, reduce extracellular norepinephrine, the impact of which may contribute to their anxiolytic actions.

IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(blockade of mGlu5 receptor decreases basal and stress-induced cortical norepinephrine in rodents)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:309170 HCAPLUS

DOCUMENT NUMBER: 142:456881

TITLE: The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles

AUTHOR(S): Varty, Geoffrey B.; Grilli, Mariagrazia; Forlani, Angelo; Fredduzzi, Silvia; Grzelak, Michael E.; Guthrie, Donald H.; Hodgson, Robert A.; Lu, Sherry X.; Nicolussi, Elisa; Pond, Annamarie J.; Parker, Eric M.; Hunter, John C.; Higgins, Guy A.; Reggiani, Angelo; Bertorelli, Rosalia

CORPORATE SOURCE: Department of Neurobiology, Schering Plough Research Institute, Kenilworth, NJ, 07033, USA

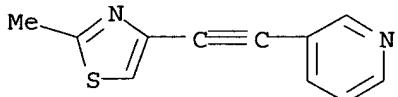
SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 207-217

PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Modulation of metabotropic glutamate receptor (mGluR) subtypes represents a novel approach for the treatment of neurol. and psychiatric disorders. This study was conducted to investigate the role of the mGluR5 and mGluR1 subtypes in the modulation of pain and anxiety. The mGluR5 antagonists, 2-methyl-6-(phenylethynyl)pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), and the mGluR1 antagonist, (4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine HCl (LY456236), were tested in models of pain [mouse formalin test, rat spinal nerve ligation (SNL)] and anxiety [Vogel conflict, conditioned lick suppression (CLS)], and their efficacious effects were compared to any associated side effects. The systemic administration of MPEP, MTEP, and LY456236 reduced hyperalgesia induced by formalin and mech. allodynia following SNL. However, only LY456236 completely reversed the allodynia. In the anxiety models, MPEP (3-30 mg/kg), MTEP (3-10 mg/kg), and LY456236 (10-30 mg/kg) produced anxiolytic-like effects similar to the benzodiazepine, chlordiazepoxide (CDP, 6 mg/kg). However, only MPEP and MTEP were able to produce a level of anxiolysis comparable to CDP. In a series of tests examining potential side effects, MPEP and MTEP reduced body temperature and locomotor activity and impaired operant responding for food and rotarod performance at doses of 3-30 and 1-30 mg/kg, resp. LY456236 reduced operant responding at 30 mg/kg. Both mGluR5 and mGluR1 antagonists are effective in models of pain and anxiety. However, an mGluR1 antagonist was more efficacious than the 2 mGluR5 antagonists in

the pain models, which, conversely, appeared more efficacious in the anxiety models. These findings support the potential utility of mGluR5 and mGluR1 antagonists for both the treatment of chronic pain and as novel anxiolytics.

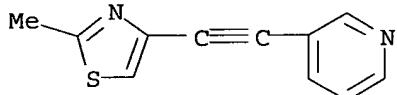
IT 329205-68-7, MTEP
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antinociceptive and anxiolytic-like effects of mGluR5 and mGluR1 antagonist, in rodents)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:227480 HCAPLUS
 DOCUMENT NUMBER: 143:19795
 TITLE: Effects of mGlu1 and mGlu5 receptor antagonists on negatively reinforced learning
 AUTHOR(S): Gravius, A.; Pietraszek, M.; Schaefer, D.; Schmidt, W. J.; Danysz, W.
 CORPORATE SOURCE: Preclinical R & D, Merz Pharmaceuticals, Frankfurt am Main, Germany
 SOURCE: Behavioural Pharmacology (2005), 16(2), 113-121
 CODEN: BPHEL; ISSN: 0955-8810
 PUBLISHER: Lippincott Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Effects on aversive learning of the novel highly selective mGlu5 receptor antagonist [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) and mGlu1 receptor antagonist (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) were tested, after systemic administration, in the passive avoidance (PA) and fear potentiated startle (FPS) paradigms. Both MTEP at 10 mg/kg and EMQMCM at 5 and 10 mg/kg, given 30 min before training, impaired acquisition of the passive avoidance response (PAR). Co-administration of MTEP and EMQMCM at doses ineffective when administered alone, produced anterograde amnesia when given 30 min before the acquisition phase. Neither EMQMCM (5 mg/kg) nor MTEP (10 mg/kg) impaired retention of the PAR after direct post-training injections. EMQMCM (5 mg/kg), but not MTEP (10 mg/kg) blocked the PAR when given 30 min before testing. Pre-training administration of MTEP at doses of 2.5 and 5 mg/kg inhibited fear conditioning in the FPS when tested 24 h later. In contrast, EMQMCM was ineffective. Our findings suggest diverse involvement of mGlu1 and mGlu5 receptors in neg. reinforced learning.
 IT 329205-68-7, MTEP
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (MTEP with EMQMCM produced dose-dependent amnesia, had no effect on consolidation, EMQMCM but not MTEP impair memory when given before retention suggesting its diverse involvement in neg.

reinforced learning in rat)
 RN 329205-68-7 HCPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 26 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:117701 HCPLUS

DOCUMENT NUMBER: 142:348844

TITLE: The mGlu5 receptor antagonists MPEP and MTEP attenuate behavioral signs of morphine withdrawal and morphine-withdrawal-induced activation of locus coeruleus neurons in rats

AUTHOR(S): Rasmussen, Kurt; Martin, Heidi; Berger, James E.; Seager, Matthew A.

CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Co., Indianapolis, IN, 46285, USA

SOURCE: Neuropharmacology (2005), 48(2), 173-180
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB N-Methyl--aspartate (NMDA) antagonists have been demonstrated to suppress the signs of opiate withdrawal; however, side effects limit their clin. use. Since the metabotropic glutamate (mGlu) 5 receptor has been shown to affect glutamate release and modulate NMDA receptor function, we examined the effects of two selective mGlu5 receptor antagonists, 2-methyl-6-(phenyl-ethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), on morphine withdrawal.

Pretreatment with MPEP or MTEP (1, 3, and 10 mg/kg, i.p.) significantly attenuated behavioral signs of morphine withdrawal.

Specifically, both MPEP and MTEP attenuated the occurrence/severity of chews, digging, salivation, and weight loss, and increased the occurrence of erections. Neither compound changed the occurrence of wet-dog shakes, ptosis, irritability, or lacrimation. Both MPEP and MTEP produced a modest, but significant, attenuation of morphine-withdrawal-induced activation of locus coeruleus neurons in anesthetized rats. These results indicate a role for mGlu5 receptors in morphine withdrawal and suggest the potential for mGlu5 antagonists in the treatment of withdrawal from opiates and other drugs of abuse.

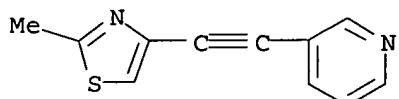
IT 329205-68-7, MTEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mGlu5 receptor antagonists MPEP and MTEP attenuate behavioral signs of morphine withdrawal and morphine-withdrawal-induced activation of locus coeruleus neurons in rats)

RN 329205-68-7 HCPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:1053982 HCAPLUS

DOCUMENT NUMBER: 142:69077

TITLE: Assessing the role of metabotropic glutamate receptor 5 in multiple nociceptive modalities

AUTHOR(S): Zhu, Chang Z.; Wilson, Sonya G.; Mikusa, Joseph P.; Wismer, Carol T.; Gauvin, Donna M.; Lynch, James J.; Wade, Carrie L.; Decker, Michael W.; Honore, Prisca

CORPORATE SOURCE: Neuroscience Research, Global Pharmaceutical Research and Development, Dept. 4N5, Bldg. AP9A, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA

SOURCE: European Journal of Pharmacology (2004), 506(2), 107-118

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

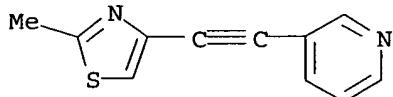
AB Preclin. data, performed in a limited number of pain models, suggest that functional blockade of metabotropic glutamate (mGlu) receptors may be beneficial for pain management. In the present study, effects of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective mGlu5 receptor antagonist, were examined in a wide variety of rodent nociceptive and hypersensitivity models to fully characterize the potential analgesic profile of mGlu5 receptor blockade. Effects of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), as potent and selective as MPEP at mGlu5/mGlu1 receptors but more selective than MPEP at N-methyl-aspartate (NMDA) receptors, were also evaluated in selected nociceptive and side effect models. MPEP (3-30 mg/kg, i.p.) produced a dose-dependent reversal of thermal and mech. hyperalgesia following complete Freund's adjuvant (CFA)-induced inflammatory hypersensitivity. Addnl., MPEP (3-30 mg/kg, i.p.) decreased thermal hyperalgesia observed in carrageenan-induced inflammatory hypersensitivity without affecting paw edema, abolished acetic acid-induced writhing activity in mice, and was shown to reduce mech. allodynia and thermal hyperalgesia observed in a model of post-operative hypersensitivity and formalin-induced spontaneous pain. Furthermore, at 30 mg/kg, i.p., MPEP significantly attenuated mech. allodynia observed in three neuropathic pain models, i.e. spinal nerve ligation, sciatic nerve constriction and vincristine-induced neuropathic pain. MTEP (3-30 mg/kg, i.p.) also potently reduced CFA-induced thermal hyperalgesia. However, at 100 mg/kg, i.p., MPEP and MTEP produced central nerve system (CNS) side effects as measured by rotarod performance and exploratory locomotor activity. These results suggest a role for mGlu5 receptors in multiple nociceptive modalities, though CNS side effects may be a limiting factor in developing mGlu5 receptor analgesic compds.

IT 329205-68-7, MTEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(assessing the role of metabotropic glutamate receptor 5 in multiple nociceptive modalities)

RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:1006680 HCAPLUS

TITLE: Anxiolytic-like effects of MTEP, a potent and selective mGlu5 receptor antagonist does not involve GABA_A signaling [Neuropharmacology 47 (2004) 342-350]

AUTHOR(S): Kłodzinska, Aleksandra; Tatarczyńska, Ewa; Chojnacka-Wojcik, Ewa; Nowak, Gabriel; Cosford, Nicholas D. P.; Pilc, Andrzej

CORPORATE SOURCE: Institute of Pharmacology, Department of Neurobiology, Polish Academy of Sciences, Krakow, 31343, Pol.

SOURCE: Neuropharmacology (2004), 47(7), 1115
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; Errata

LANGUAGE: English

AB Unavailable

L9 ANSWER 29 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:870789 HCAPLUS

DOCUMENT NUMBER: 142:212131

TITLE: The Behavioral Profile of the Potent and Selective mGlu5 Receptor Antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) in Rodent Models of Anxiety

AUTHOR(S): Busse, Chris S.; Brodkin, Jesse; Tattersall, David; Anderson, Jeffery J.; Warren, Noelle; Tehrani, Lida; Bristow, Linda J.; Varney, Mark A.; Cosford, Nicholas D. P.

CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, USA

SOURCE: Neuropsychopharmacology (2004), 29(11), 1971-1979

CODEN: NEROEW; ISSN: 0893-133X

PUBLISHER: Nature Publishing Group

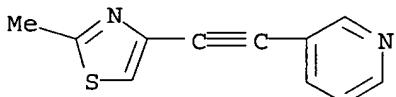
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous reports have demonstrated the anxiolytic effect of the potent and systemically active metabotropic glutamate subtype 5 (mGlu5) receptor antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) in rodents. Here, we present evidence for the anxiolytic activity of a novel mGlu5 receptor antagonist, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), in rats and compare its profile to the benzodiazepine receptor agonist diazepam. MTEP occupied mGlu5 receptors in a dose-dependent manner with essentially full receptor occupancy at the highest dose tested (10 mg/kg, i.p.). At doses appropriate for mGlu5 receptor-mediated effects, MTEP significantly reduced fear-potentiated startle and increased punished responding in a modified Geller-Seifter conflict model consistent with an anxiolytic-like profile. In both models, the magnitude

of the anxiolytic-like response was similar to that seen with diazepam. In contrast, MTEP decreased unpunished responding to a lesser extent than diazepam and had no effect on rotarod performance when administered either alone or in combination with ethanol. Repeated dosing with MTEP in this model eliminated the increase in punished responding observed with acute dosing. The present results suggest that mGlu5 receptor antagonists lack the side effects seen with benzodiazepines, such as sedation and ethanol interaction, and provide insight into a possible role for mGlu5 receptor antagonists in the modulation of mood disorders.

IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGlu5 receptor antagonist MTEP showed anxiolytic effect similar to diazepam and also displayed efficacy in anxiety with no interaction with ethanol, reduced propensity to induce motor impairment in rat model of anxiety)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



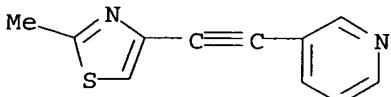
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 30 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:654838 HCAPLUS
 DOCUMENT NUMBER: 141:325154
 TITLE: Discovery of Novel Heteroarylazoles That Are Metabotropic Glutamate Subtype 5 Receptor Antagonists with Anxiolytic Activity
 AUTHOR(S): Roppe, Jeffrey; Smith, Nicholas D.; Huang, Dehua; Tehrani, Lida; Wang, Bowei; Anderson, Jeffrey; Brodkin, Jesse; Chung, Janice; Jiang, Xiaohui; King, Christopher; Munoz, Benito; Varney, Mark A.; Prasit, Petpiboon; Cosford, Nicholas D. P.
 CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, 92121, USA
 SOURCE: Journal of Medicinal Chemistry (2004), 47(19), 4645-4648
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 141:325154
 AB The highly potent, selective, and brain-penetrant metabotropic glutamate subtype 5 (mGlu5) receptor antagonists 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile and 3-fluoro-5-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile are reported. Compound 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile is active in the rat fear-potentiated startle (FPS) model of anxiety with ED₅₀ = 5.4 mg/kg (po) when dosed acutely. In this model the anxiolytic effects of 3-(5-pyridin-2-yl-2H-tetrazol-2-yl)benzonitrile rapidly tolerate on repeated dosing.
 IT 329205-68-7
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(discovery of novel heteroarylazoles that are metabotropic glutamate subtype 5 receptor antagonists with anxiolytic activity)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:604070 HCAPLUS

DOCUMENT NUMBER: 141:236331

TITLE: Anxiolytic-like effects of MTEP, a potent and selective mGlu5 receptor agonist does not involve GABA signaling

AUTHOR(S): Kłodzinska, Aleksandra; Tatarczyńska, Ewa; Chojnacka-Wojcik, Ewa; Nowak, Gabriel; Cosford, Nicholas D. P.; Pilc, Andrzej

CORPORATE SOURCE: Institute of Pharmacology, Department of Neurobiology, Polish Academy of Sciences, Krakow, 31343, Pol.

SOURCE: Neuropharmacology (2004), 47(3), 342-350
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

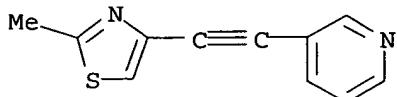
AB Several lines of evidence suggest a crucial involvement of glutamate in the mechanism of action of anxiolytic drugs including the involvement of group I metabotropic glutamate (mGlu) receptors. Given the recent discovery of a selective and brain penetrable mGlu5 receptor antagonists, the effect of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP), i.e. the most potent mGlu5 antagonist, was evaluated in established models of anxiety after single or repeated administration. We also studied if the anxiolytic effect of MTEP is mediated by mechanism involving the GABA-benzodiazepine (BZD) receptor complex. Expts. were performed on male Wistar rats or male Albino Swiss mice. The anxiolytic-like effects of MTEP were tested in the conflict drinking test and the elevated plus-maze test in rats as well as in the four-plate test in mice. MTEP (0.3-3.0 mg/kg) induced anxiolytic-like effects in the conflict drinking test (after single and repeated administration) and in the elevated plus-maze test in rats. In the four-plate test in mice, it exerted anxiolytic activity at a dose of 20 mg/kg. MTEP had no effect on the locomotor activity of animals. The anxiolytic-like effect of MTEP was not changed by BZD antagonist flumazenil. Moreover, a synergistic interaction between non-EDs of MTEP and diazepam was observed in the conflict drinking test. These data suggest that selective mGlu5 receptor antagonists mediated anxiolysis is not dependent on GABAergic system and that these agents may play a role in the therapy of anxiety.

IT 329205-68-7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anxiolytic-like effects of MTEP does not involve GABA signaling)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 32 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:523298 HCAPLUS

DOCUMENT NUMBER: 141:133562

TITLE: 5-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-2,3'-bipyridine: a highly potent, orally active metabotropic glutamate subtype 5 (mGlu5) receptor antagonist with anxiolytic activity

AUTHOR(S): Roppe, Jeffrey R.; Wang, Bowei; Huang, Dehua; Tehrani, Lida; Kamenecka, Theodore; Schweiger, Edwin J.; Anderson, Jeffery J.; Brodkin, Jesse; Jiang, Xiaohui; Cramer, Merryl; Chung, Janice; Reyes-Manalo, Grace; Munoz, Benito; Cosford, Nicholas D. P.

CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, San Diego, CA, 92121, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(15), 3993-3996

CODEN: BMCL8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 141:133562

AB Structure-activity relation studies leading to the discovery of a new, orally active mGlu5 receptor antagonist are described. The title compound, 5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-2,3'-bipyridine, is highly potent in vitro, has good in vivo receptor occupancy, and is efficacious in the rat fear-potentiated startle model of anxiety following oral dosing.

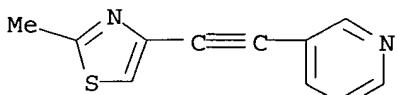
IT 329205-68-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and structure activity relations of [(methylthiazolyl)ethynyl]bipyridines as potent, orally active metabotropic glutamate subtype 5 receptor antagonist with anxiolytic activity)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 33 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

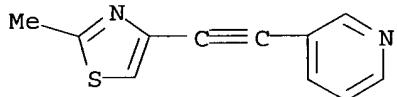
ACCESSION NUMBER: 2004:486983 HCAPLUS

DOCUMENT NUMBER: 141:235688

TITLE: Inhibition of human hepatic CYP isoforms by mGluR5 antagonists
 AUTHOR(S): Green, Mitchell D.; Jiang, Xiaohui; King, Christopher D.
 CORPORATE SOURCE: Merck Research Laboratories San Diego, San Diego, CA, 92121, USA
 SOURCE: Life Sciences (2004), 75(8), 947-953
 CODEN: LIFSAK; ISSN: 0024-3205
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Characterization of new chemical entities for their potential to produce drug-drug interactions is an important aspect of early drug discovery screening. In the present study, the potential for three metabotropic glutamate receptor antagonists to interact with recombinant human CYPs was investigated. 2-Methyl-6-(phenylethynyl)pyridine (SIB-1893), 2-methyl-6-(phenylethynyl) pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) were moderate competitive inhibitors of recombinant human CYP1A2 (K_i , 0.5-1 μ M). SIB-1893, but not MPEP or MTEP, was also a moderate competitive inhibitor of CYP1B1. MPEP and MTEP were weak inhibitors of CYP2C19. None of the three compds. tested were significant inhibitors (IC_{50} values >50 μ M) of CYP3A4, 2C9, 2D6, 2A6, 2B6 or 2E1. The results suggest that MTEP is a selective inhibitor of CYP1A2 and may prove to be a useful tool in studying drug-drug interactions involving this enzyme.

IT 329205-68-7, MTEP
 RL: PAC (Pharmacological activity); BIOL (Biological study)
 (inhibition of human hepatic CYP isoforms by mGluR5 antagonists)
 RN 329205-68-7 HCAPLUS
 CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:567590 HCAPLUS
 DOCUMENT NUMBER: 139:391590
 TITLE: In vivo receptor occupancy of mGlu5 receptor antagonists using the novel radioligand [³H]3-methoxy-5-(pyridin-2-ylethynyl)pyridine)
 AUTHOR(S): Anderson, Jeffery J.; Bradbury, Margaret J.; Giracello, Darlene R.; Chapman, Deborah F.; Holtz, Greg; Roppe, Jeffrey; King, Chris; Cosford, Nicholas D. P.; Varney, Mark A.
 CORPORATE SOURCE: MRLSDB1, Department of Neuropharmacology, Merck Research Laboratories, San Diego, CA, 92121, USA
 SOURCE: European Journal of Pharmacology (2003), 473(1), 35-40
 CODEN: EJPHAZ; ISSN: 0014-2999
 PUBLISHER: Elsevier Science B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB In vivo receptor occupancy of mGlu5 receptor antagonists was quantified in rat and mouse brain using the mGlu5 receptor selective antagonist

[³H]3-methoxy-5-(pyridin-2-ylethynyl)pyridine ([³H]methoxy-PEPy). Administration of [³H]methoxy-PEPy (50 µCi/kg i.v.) to mGlu5 receptor-deficient mice revealed binding at background levels in forebrain, whereas wild-type mice exhibited 14-fold higher binding in forebrain relative to cerebellum. Systemic administration of the mGlu5 receptor antagonists 2-methyl-6-(phenylethynyl)pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) reduced the binding of [³H]methoxy-PEPy in rats and mice, reflecting mGlu5 receptor occupancy by these compds. MPEP (10 mg/kg i.p.) and MTEP (3 mg/kg i.p.) maintained >75% receptor occupancy for 2 h in rats, while in mice MPEP and MTEP achieved >75% occupancy for only 30 and 15 min, resp. Compound levels in plasma were substantially lower in mice suggesting species differences in receptor occupancy result from differences in absorption or metabolism of the compds. These findings demonstrate that [³H]methoxy-PEPy is useful for determining the occupancy of mGlu5 receptors in the brain.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 35 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:91263 HCAPLUS

DOCUMENT NUMBER: 138:379345

TITLE: [³H]-Methoxymethyl-MTEP and [³H]-Methoxy-PEPy: potent and selective radioligands for the metabotropic glutamate subtype 5 (mGlu5) receptor

AUTHOR(S): Cosford, Nicholas D. P.; Roppe, Jeffrey; Tehrani, Lida; Schweiger, Edwin J.; Seiders, T. Jon; Chaudary, Ashok; Rao, Sara; Varney, Mark A.

CORPORATE SOURCE: Department of Chemistry, Merck Research Laboratories, San Diego, CA, 92121, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(3), 351-354

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

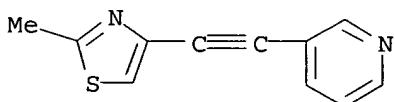
AB The design, synthesis, and characterization of two potent, non-competitive radioligands, [³H]-methoxymethyl-MTEP and [³H]-Methoxy-PEPy, that are selective for the mGlu5 receptor are described.

IT 329205-68-7P

RL: BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
([³H]-Methoxymethyl-MTEP and [³H]-Methoxy-PEPy in relation to design, synthesis and in-vitro characterization in rat brain membranes of potent and selective radioligands for metabotropic glutamate subtype-5 receptor)

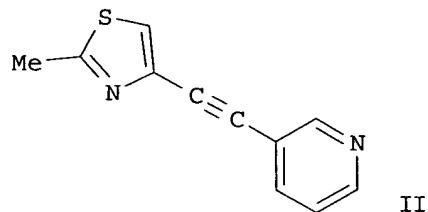
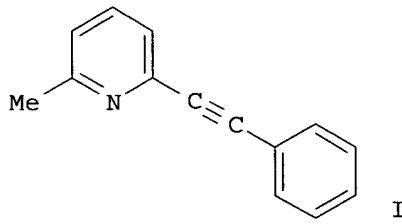
RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 36 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:943427 HCAPLUS
 DOCUMENT NUMBER: 138:170117
 TITLE: 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]- pyridine: A Potent and Highly Selective Metabotropic Glutamate Subtype 5 Receptor Antagonist with Anxiolytic Activity
 AUTHOR(S): Cosford, Nicholas D. P.; Tehrani, Lida; Roppe, Jeffrey; Schweiger, Edwin; Smith, Nicholas D.; Anderson, Jeffrey; Bristow, Linda; Brodkin, Jesse; Jiang, Xiaohui; McDonald, Ian; Rao, Sara; Washburn, Mark; Varney, Mark A.
 CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, 92121, USA
 SOURCE: Journal of Medicinal Chemistry (2003), 46(2), 204-206
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 138:170117
 GI



AB 2-Methyl-6-(phenylethynyl)pyridine (I), a potent noncompetitive mGlu5 receptor antagonist widely used to characterize the pharmacol. of mGlu5 receptors, suffers from a number of shortcomings as a therapeutic agent, including off-target activity and poor aqueous solubility. Seeking to improve

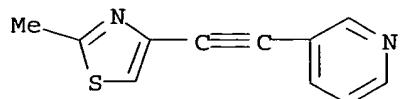
the properties of I led to the synthesis of compound II, a highly selective mGlu5 receptor antagonist that is 5-fold more potent than I in the rat fear-potentiated startle model of anxiety.

IT 329205-68-7P

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation, structure-activity relationship, and mGlu5 receptor antagonist activity of phenyl- and pyridinylethylnylthiazoles via coupling reactions of halobenzene or halopyridines with Me[(trimethylsilyl)ethynyl]thiazole)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

21

THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 37 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:932568 HCAPLUS
 DOCUMENT NUMBER: 138:379544
 TITLE: [3H]methoxymethyl-3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine binding to metabotropic glutamate receptor subtype 5 in rodent brain: in vitro and in vivo characterization
 AUTHOR(S): Anderson, Jeffery J.; Rao, Sara P.; Rowe, Blake; Giracello, Darlene R.; Holtz, Greg; Chapman, Deborah F.; Tehrani, Lida; Bradbury, Margaret J.; Cosford, Nicholas D. P.; Varney, Mark A.
 CORPORATE SOURCE: Department of Neuropharmacology, Merck Research Laboratories, San Diego, CA, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 303(3), 1044-1051
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The binding of [3H]methoxymethyl-3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (methoxymethyl-MTEP), a potent and selective antagonist for metabotropic glutamate (mGlu)5 receptors, was characterized in rat brain both in vitro and in vivo. Non-specific binding, as defined with 10 μ M 2-methyl-6-(phenylethynyl)-pyridine (MPEP), was less than 10% of total binding in rat brain membranes. The binding of [3H]methoxymethyl-MTEP was of high affinity ($K_d = 20 \pm 2.7$ nM), saturable ($B_{max} = 487 \pm 48$ fmol/mg protein), and to a single site. The mGlu5 antagonists methoxymethyl-MTEP and MPEP displaced [3H]methoxymethyl-MTEP binding with IC₅₀ values of 30 and 15 nM, resp. In vivo administration of [3H]methoxymethyl-MTEP (50 μ Ci/kg i.v.) revealed 12-fold higher binding in hippocampus (an area enriched in mGlu5 receptors) relative to cerebellum (an area with few mGlu5 receptors) in rats. Similarly, administration of [3H]methoxymethyl-MTEP to mGlu5-deficient mice demonstrated binding at background levels in forebrain, whereas wild-type littermates exhibited 17-fold higher binding in forebrain relative to cerebellum. Systemic administration of unlabeled mGlu5 antagonists methoxymethyl-MTEP and MPEP to rats reduced the binding of [3H]methoxymethyl-MTEP with ID₅₀ values of 0.8 and 2 mg/kg i.p., resp., 1 h post-treatment. The mGlu5 agonist 2-chloro-5-hydroxyphenylglycine (CHPG) (0.3, 1, and 3 μ mol) dose-dependently increased phosphoinositide (PI) hydrolysis in the hippocampus after i.c.v. administration in rats. CHPG-evoked increases in PI hydrolysis were blocked with MPEP at a dose (10 mg/kg i.p.) that markedly reduced [3H]methoxymethyl-MTEP binding in vivo. These results indicate that [3H]methoxymethyl-MTEP is a selective radioligand for labeling mGlu5 and is useful for studying the binding of mGlu5 receptors in rat brain in vitro and in vivo.
 REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 38 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:618102 HCAPLUS
 TITLE: 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP): A potent and highly selective metabotropic glutamate subtype 5 (mGlu5) receptor antagonist with anxiolytic activity
 AUTHOR(S): Cosford, Nicholas D. P.; Tehrani, Lida; Arruda, Jeannie; King, Christopher; McDonald, Ian A.; Munoz,

Benito; Roppe, Jeffrey; Schweiger, Edwin; Smith, Nicholas; Wang, Bowei; Zhang, Kanyin; Anderson, Jeffrey; Bristow, Linda; Brodkin, Jesse; Rao, Sara; Siegel, Robert; Tattersall, David; Washburn, Mark; Prasit, Peppi; Varney, Mark

CORPORATE SOURCE: Merck Research Laboratories, San Diego, San Diego, CA, 92121-1140, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-251. American Chemical Society: Washington, D. C.

CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Glutamate is the principle excitatory transmitter in the central nervous system acting through ionotropic glutamate receptors; however, it also plays a major role in activating modulatory pathways through G protein-coupled metabotropic glutamate (mGlu) receptors. Group I mGlu receptors include mGlu1 and mGlu5 which are coupled to stimulation of phospholipase C resulting in phosphoinositide hydrolysis and elevation of intracellular Ca²⁺ levels ([Ca²⁺]_i). Excessive activation of mGlu5 has been implicated in several diseases, and selective mGlu5 antagonists may be of therapeutic benefit in the treatment of various pain states, neurol. impairments and psychiatric disorders such as anxiety and depression. MPEP (1) was recently discovered to be a potent non-competitive mGlu5 receptor antagonist which has been used by several research groups to characterize the pharmacol. and neurobiol. of mGlu5 receptors. As a potential drug mol., however, MPEP suffers from a number of shortcomings. These include off-target activity and poor aqueous solubility (high LogD) leading

to low CSF levels with, consequently, relatively low in vivo efficacy. Seeking to improve on the properties of 1 led to the identification of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) (2), a highly selective mGlu5 receptor antagonist that is five-fold more potent than MPEP in the rat fear-potentiated startle model of anxiety. Details of the SAR leading to the discovery of MTEP and the pharmacol. profile of this new mGlu5 receptor antagonist will be presented.

L9 ANSWER 39 OF 45 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:433449 HCPLUS

DOCUMENT NUMBER: 137:209145

TITLE: Magnetothermopower study of the quasi-two-dimensional organic conductor α -(BEDT-TTF)2KHg(SCN)4

AUTHOR(S): Choi, E. S.; Brooks, J. S.; Qualls, J. S.

CORPORATE SOURCE: Department of Physics, Ewha Womans University, Seoul, 120-750, S. Korea

SOURCE: Physical Review B: Condensed Matter and Materials Physics (2002), 65(20), 205119/1-205119/11

CODEN: PRBMDO; ISSN: 0163-1829

PUBLISHER: American Physical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have used a low-frequency magneto-thermopower (MTEP) method to probe the high-magnetic-field ground-state behavior of α -(BEDT-TTF)2KHg(SCN)4 along all three principal crystallog. axes at low temps. The thermopower tensor coeffs. (Sxx, Syx, and Szz) have been measured to 30 T, beyond the anomalous low-temperature, field-induced transition

at 22.5 T. The authors find a significant anisotropy in the MTEP signal, and also observe large quantum oscillations associated with Landau

quantization. The anisotropy indicates that the ground-state properties are clearly driven by mechanisms that occur along specific directions for the in-plane electronic structure. Both transverse and longitudinal magnetothermopower show asymptotic behaviors in the field, which can be explained in terms of magnetic breakdown of compensated closed orbits.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 40 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:305803 HCAPLUS
 DOCUMENT NUMBER: 135:69001
 TITLE: Magnetothermopower study of quasi-two-dimensional organic conductor α -(BEDT-TTF)2KHg(SCN)4
 Choi, E. S.; Brooks, J. S.; Qualls, J. S.
 CORPORATE SOURCE: Department of Physics, Ewha Womans University, Seoul, 120-750, S. Korea
 SOURCE: Los Alamos National Laboratory, Preprint Archive, Condensed Matter (2001) 1-22, arXiv:cond-mat/0104447, 24 Apr 2001
 CODEN: LNCMFR
 URL: <http://xxx.lanl.gov/pdf/cond-mat/0104447>
 PUBLISHER: Los Alamos National Laboratory
 DOCUMENT TYPE: Preprint
 LANGUAGE: English

AB The authors have used a low-frequency magneto-thermopower (MTEP) method to probe the high magnetic field ground state behavior of α -(BEDT-TTF)2KHg(SCN)4 along all three principal crystallog. axes at low temps. The thermopower tensor coeffs. (Sxx, Syx, and Szz) have been measured to 30 T, beyond the anomalous low temperature, field-induced transition

at 22.5 T. The authors find a significant anisotropy in the MTEP signal, and also observe large quantum oscillations associated with the de Haas-van Alphen effect. The anisotropy indicates that the ground state properties are clearly driven by mechanisms that occur along specific directions for the in-plane electronic structure. Both the transverse and longitudinal magnetothermopower show asymptotic behavior in field, which can be explained in terms of magnetic breakdown of compensated closed orbits.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

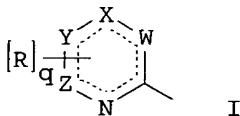
L9 ANSWER 41 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:167983 HCAPLUS
 DOCUMENT NUMBER: 134:222706
 TITLE: Preparation of heterocyclic compounds as metabotropic glutamate receptor 5 (mGluR5) modulators
 INVENTOR(S): Cosford, Nicholas D. P.; McDonald, Ian A.; Bleicher, Leo Solomon; Cube, Rowena V.; Schweiger, Edwin J.; Vernier, Jean-Michel; Hess, Stephen D.; Varney, Mark A.; Munoz, Benito
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: PCT Int. Appl., 132 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001016121	A1	20010308	WO 2000-US23923	20000831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6956049	B1	20051018	US 1999-387135	19990831
CA 2383524	AA	20010308	CA 2000-2383524	20000831
EP 1214303	A1	20020619	EP 2000-957932	20000831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003508390	T2	20030304	JP 2001-519688	20000831
AU 780009	B2	20050224	AU 2000-69482	20000831
PRIORITY APPLN. INFO.:			US 1999-387073	A2 19990831
			US 1999-387135	A2 19990831
			WO 2000-US23923	W 20000831

OTHER SOURCE(S) : MARPAT 134:222706

GI



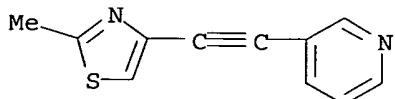
AB The title compds. I [ALB; A = 5-7 membered ring II (wherein at least one of W, X, Y and Z = (CR)p; p = 0-2, and the remainder of W, X, Y and Z = O, N, S; R = halo, (un)substituted aryl, heterocyclyl, etc.); L = (un)substituted alkenylene, alkynylene, azo; B = (un)substituted alkyl, cycloalkyl, heterocyclyl, etc.] and their pharmaceutically acceptable salts which are capable of modulating the activity of excitatory amino acid receptors such as metabotropic glutamate receptor, were prepared. Thus, reacting 2-bromo-1,3-thiazole with phenylacetylene in the presence of CuI, Et₃N and PdCl₂(PPh₃)₂ in DME followed by treatment of the resulting 2-(phenylethynyl)-1,3-thiazole with p-TsOH afforded 2-(phenylethynyl)-1,3-thiazole, p-TsOH salt which showed IC₅₀ of 0.1 nM - 10 μM in Ca⁺² flux assay and analgesic efficacy in analgesic animal model (CFA model).

IT 329205-68-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic compds. as metabotropic glutamate receptor 5 (mGluR5) modulators)

RN 329205-68-7 HCAPLUS

CN Pyridine, 3-[(2-methyl-4-thiazolyl)ethynyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

DOCUMENT TYPE: Journal
 LANGUAGE: Russian
 AB The longitudinal magnetothermoelec. power (MTEP) was calculated for metals in a magnetic field and in the vicinity of the electronic topol. transition. Giant oscillations of MTEP as functions of the applied magnetic field strength are found. The oscillations are due to the energy dependence of the electron relaxation time in a magnetic field, and they are inherent in any normal metal irresp. of the shape of the Fermi surface. Nevertheless, the electronic topol. transition alters essentially both shape and amplitude of such oscillations. The results of recent exptl. investigations of MTEP in Cd crystals under pressure and in a magnetic field are discussed in terms of the theory.

L9 ANSWER 45 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1989:23982 HCAPLUS
 DOCUMENT NUMBER: 110:23982
 TITLE: Neighboring group participation in organic redox reactions. 13. Intramolecular interaction of the β -phosphonic acid group in the aqueous iodine oxidation of thio ethers and disulfides. Generation of a phosphonic-phosphoric anhydride
 AUTHOR(S): Doi, Joyce Takahashi; Musker, W. Kenneth
 CORPORATE SOURCE: Dep. Chem., Univ. California, Davis, CA, 95616, USA
 SOURCE: Phosphorus and Sulfur and the Related Elements (1988), 35(1-2), 173-82
 CODEN: PREEDF; ISSN: 0308-664X

DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 110:23982
 AB The oxidation of the phosphonic acid-thio ether, 2-methylthioethanephosphonic acid (MTEP) and the oxidative cleavage of the phosphonic acid-disulfide, bis(2-phosphonoethyl) disulfide (PED), by aqueous iodine are accelerated by neighboring group participation. The pH profiles indicate that in both cases it is the dianionic form of the phosphonate group which is responsible for accelerations of 106 and 102 in the reactions of MTEP and PED, resp., compared to analogs without neighboring groups. The oxidative cleavage of PED in the presence of phosphate buffer generates .apprx.30% of a hydrolytically stable, mixed phosphonic-phosphoric anhydride, which makes the proposed cyclic sulfenic-phosphonic anhydride intermediate one of the more efficient phosphate coupling agents in aqueous solution. In contrast, no mixed anhydride is generated during the oxidation of MTEP in phosphate buffer.

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=> d stat que 114
L1      1 SEA FILE=REGISTRY ABB=ON PLU=ON MTEP/BI
L2          SEL PLU=ON L1 1- CHEM :           2 TERMS
L3      46 SEA FILE=HCAPLUS ABB=ON PLU=ON L2
L4          46 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR MTEP
L5      34433 SEA FILE=HCAPLUS ABB=ON PLU=ON ("OVERACTIVE BLADDER"/CV OR
          "BLADDER, DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7      148785 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR URINARY? OR ?CYSTITIS?
          OR URINE(2A) LEAK? OR ENURESIS OR BED(W) WETTING
L8          1 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND L7
L9          45 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 NOT L8
L12         33 SEA FILE=HCAPLUS ABB=ON PLU=ON PYRIDIN? (L) METHYL(L) THIAZOL? (L
          ) ETHYN?
L14         6 SEA FILE=HCAPLUS ABB=ON PLU=ON L12 NOT (L8 OR L9)
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RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 42 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:897565 HCAPLUS
 DOCUMENT NUMBER: 123:356291
 TITLE: On the sign of thermoelectric power of GMR multilayers
 AUTHOR(S): Sakurai, Junji; Hasegawa, Katsuhiro; Shintaku,
 Kazuhiko; Shinjo, Teruya
 CORPORATE SOURCE: Dep. Physics, Toyama Univ., Toyama, 930, Japan
 SOURCE: Journal of the Physical Society of Japan (1995),
 64(10), 3897-902
 CODEN: JUPSAU; ISSN: 0031-9015
 PUBLISHER: Physical Society of Japan
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The thermoelec. power S of artificial magnetic multilayers of Fe/Au was measured as functions of temperature T as well as magnetic field H. The magnetothermoelec. power (MTEP) has a neg. sign. Data of S of magnetic multilayers of Co/Cu hitherto published were reexamnd. in order of clarify its sample dependence, and MTEP for these multilayers was ascertained to have also a neg. sign. The neg. sign of MTEP of the 2 systems are discussed in relation to the theory developed by Inoue et al.

L9 ANSWER 43 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1992:502248 HCAPLUS
 DOCUMENT NUMBER: 117:102248
 TITLE: Large magnetothermoelectric power in cobalt/copper,
 iron/copper, and iron/chromium multilayers
 AUTHOR(S): Piraux, L.; Fert, A.; Schroeder, P. A.; Loloe, R.;
 Etienne, P.
 CORPORATE SOURCE: Unite Phys.-Chim. Phys. Mater., Univ. Cathol. Louvain,
 Louvain-la-Neuve, B-1348, Belg.
 SOURCE: Journal of Magnetism and Magnetic Materials (1992),
 110(3), L247-L253
 CODEN: JMMMD; ISSN: 0304-8853
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The authors report and discuss exptl. data on the thermoelec. power of magnetic multilayers. Measurements of the thermoelec. power of Fe/Cr, Co/Cu, and Fe/Cu multilayers were carried out at 4-150 K in magnetic fields perpendicular to the layers. All specimens exhibit pronounced magnetothermoelec. power (MTEP) effects correlating with their giant neg. magnetoresistance. Whereas the magnetoresistance is a decreasing function of temperature, the MTEP, at least in Co/Cu and Fe/Cu multilayers, is very small at low temperature and increases rapidly above 30-40 K. This high temperature part of the MTEP is due to spin-dependent electron-magnon scattering.

L9 ANSWER 44 OF 45 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1990:489423 HCAPLUS
 DOCUMENT NUMBER: 113:89423
 TITLE: Giant oscillations of magnetothermoelectric power of metals in the vicinity of the electronic topological transition
 AUTHOR(S): Blanter, Ya. M.; Varlamov, A. A.; Pantsulaya, A. V.
 CORPORATE SOURCE: Mosk. Inst. Stali Splavov, Moscow, USSR
 SOURCE: Zhurnal Eksperimental'noi i Teoreticheskoi Fiziki
 (1990), 97(4), 1237-53
 CODEN: ZETFA7; ISSN: 0044-4510

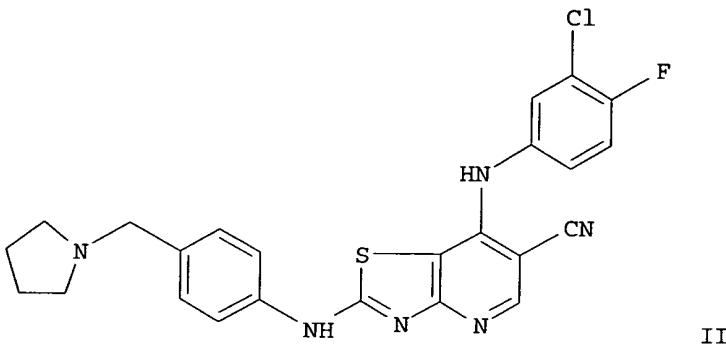
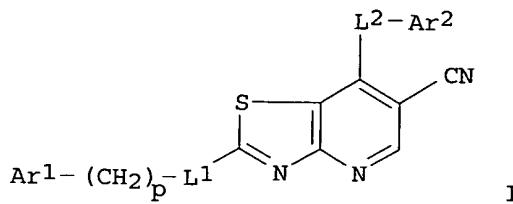
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L14 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:231127 HCAPLUS
 DOCUMENT NUMBER: 144:312078
 TITLE: Preparation of thiazolopyridine protein kinase
 inhibitors useful against various tumors
 INVENTOR(S): Connolly, Peter J.; Johnson, Sigmond G.; Pandey,
 Niranjan B.; Middleton, Steven A.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 74 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006058341	A1	20060316	US 2005-226961	20050915
WO 2006031929	A2	20060323	WO 2005-US32837	20050915
WO 2006031929	A3	20060601		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: US 2004-609992P P 20040915
 OTHER SOURCE(S): MARPAT 144:312078
 GI

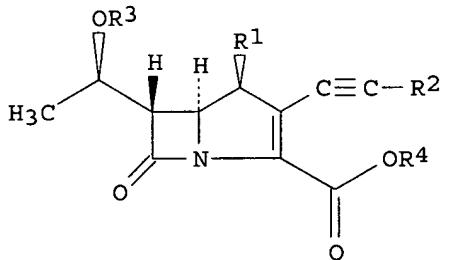


AB The present invention is directed to novel thiazolopyridines (shown as I; variables defined below; e.g. 7-(3-chloro-4-fluorophenylamino)-2-[(4-[(pyrrolidin-1-yl)methyl]phenyl)amino]thiazolo[4,5-b]pyridine-6-carbonitrile dihydrochloride (free base shown as II)), pharmaceutical compns. thereof, and the use thereof as inhibitors of ATP-protein kinase interactions. For I: L1 = S(C1-4alkyl), a bond, N(R1), N(R1)C(O) and C(O)N(R1), wherein R1 = H, C1-8alkyl and C1-8alkyl(C1-8alkoxy); p = 0-4; L2 = O, S, N(R1) and a bond; Ar1 = aryl, heteroaryl, benzofused heteroaryl, heterocyclyl and benzofused heterocyclyl (un)substituted with 1-3 substituents; and Ar2 = aryl, heteroaryl, benzofused heteroaryl, heterocyclyl and benzofused heterocyclyl (un)substituted with 1-3 substituents; addnl. details are given in the claims. Methods of preparation are claimed and preps. and/or characterization data for apprx. 50 examples of I are included. For example, II was prepared in 7 steps starting with preparation of 4-chloro-2-cyano-3-hydroxybut-2-enoic acid tert-Bu ester from tert-Bu cyanoacetate and chloroacetyl chloride and involving the following addnl. intermediates: N-tert-butyl-4-chloro-3-oxobutyramide, 3-(4-amino-2-methylsulfanylthiazol-5-yl)-N-tert-butyl-3-oxopropionamide, 7-chloro-2-methylsulfanylthiazolo[4,5-b]pyridine-6-carbonitrile, 7-(3-chloro-4-fluorophenylamino)-2-methylsulfanylthiazolo[4,5-b]pyridine-6-carbonitrile, and [4-[(pyrrolidin-1-yl)methyl]phenyl]amine. IC50 values for inhibition by some examples of I of EGFR, HER-2, c-Src and Lyn kinases are tabulated.

L14 ANSWER 2 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:671910 HCPLUS
 DOCUMENT NUMBER: 143:172679
 TITLE: 2-Ethynylcarbapenem derivatives and process for their preparation
 INVENTOR(S): Maruyama, Takahisa; Aihara, Kazuhiro
 PATENT ASSIGNEE(S): Meiji Seika Kaisha, Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 26 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2005200412	A2	20050728	JP 2004-365408	20041217
PRIORITY APPLN. INFO.:			JP 2003-421811	A 20031219
OTHER SOURCE(S):	MARPAT	143:172679		
GI				



AB Title compds. I [R1 = Me, H; R2 = H, (un)substituted pyridine, etc.; R3 = H, 4-nitrobenzyloxycarbonyl, etc.; R4 = H, 4-nitrobenzyl, etc.] were prepared. Process for producing compound I [R1, R2, R3, R4 = same as above] via Pd catalyzed coupling reaction was provided. For example, to a solution of (1S,5R,6S)-2-ethynyl-1-methyl-6-((1R)-1-triethylsilyloxyethyl)-1-carbapen-2-em-3-carboxylic acid 4-nitrobenzyl ester (807 mg) in DMF (10 mL) were added 2-iodoimidazo[5,1-b]thiazole (416 mg), dichloro[bis(triphenylphosphine)]palladium (23 mg), CuI (3 mg) and triethylamine (0.47 mL). The reaction was then stirred at 35 °C for 30 min., followed by aqueous work-up and silica-gel purification to give (1S,5R,6S)-2-[imidazo[5,1-b]thiazol-2-ylethylyn]-1-methyl-6-((1R)-1-triethylsilyloxyethyl)-1-carbapen-2-em-3-carboxylic acid 4-nitrobenzyl ester (II) (960 mg). Desilylation of compound II using HCl and treatment with sodium phosphate buffer/zinc powder afforded (1S,5R,6S)-6-((1R)-1-hydroxyethyl)-2-[imidazo[5,1-b]thiazol-2-ylethylyn]-1-methyl-1-carbapen-2-em-3-carboxylic acid sodium salt (III). In antibacterial activity assays, the MIC value of compound III against *Streptococcus pneumoniae* 197 (PRSP) was 0.25 µg/mL. Compds. I are claimed useful as antibacterial agents.

L14 ANSWER 3 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:120856 HCPLUS
 DOCUMENT NUMBER: 140:163889
 TITLE: Preparation of condensed pyridines and pyrimidines as Tie2 receptor tyrosine kinase inhibitors and their anti-angiogenic effect
 INVENTOR(S): Luke, Richard William Arthur; Jones, Clifford David; McCoull, William; Hayter, Barry Raymond
 PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
 SOURCE: PCT Int. Appl., 184 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004013141	A1	20040212	WO 2003-GB3275	20030801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2494421	AA	20040212	CA 2003-2494421	20030801
AU 2003246972	A1	20040223	AU 2003-246972	20030801
EP 1537112	A1	20050608	EP 2003-766443	20030801
EP 1537112	B1	20060419		
R: AT, BE, CH, DE, DK, ES, FR, IE, SI, LT, LV, FI, RO, MK	GB, GR, IT, LI, LU, NL, SE, MC, PT, CY, AL, TR, BG, CZ, EE, HU, SK			
BR 2003013078	A	20050712	BR 2003-13078	20030801
CN 1688579	A	20051026	CN 2003-823754	20030801
JP 2005538118	T2	20051215	JP 2004-525533	20030801
AT 323702	E	20060515	AT 2003-766443	20030801
NO 2005000418	A	20050428	NO 2005-418	20050125
US 2005256140	A1	20051117	US 2005-523401	20050203
PRIORITY APPLN. INFO.:			GB 2002-18168	A 20020806
			GB 2003-12356	A 20030530
			WO 2003-GB3275	W 20030801

OTHER SOURCE(S) : MARPAT 140:163889
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

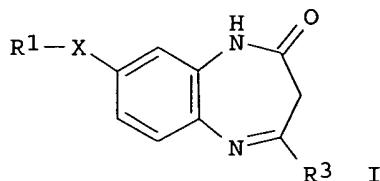
AB Title compds. I [wherein ACC = fused 5-membered heteroaryl ring; G = O, S and NH and derivs.; Z = N and CH and derivs.; Q1 = (un)substituted hetero/aryl; R1 = H, halo, CF₃, CN, NO₂, OH and derivs., NH₂ and derivs., SH and derivs., N-alkyl/N,N-dialkyl/carbamoyl, alk(en/yn)yl, N-alkyl/alkanesulfonylamino, N-alkylsulfamoyl, etc.; R2 = H, , OH, halo, alkyl, alkoxy, formyl, alkyl/dialkyl/amino; R3 = independently as defined for R4, provided that R3 is not H, and when R3 is attached to a N atom in A, R3 is not halo; R4 = H, halo, CF₃, OCF₃, CN, NC, NO₂, OH and derivs., SH and derivs., NH₂ and derivs., formyl, CO₂H and derivs., carbamoyl, N-alkyl/N,N-dialkyl/sulfamoyl, alk(en/yn)yl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, alkanesulfonylamino, etc.] were prepared as Tie2 receptor tyrosine kinase inhibitors for use in the production of an anti-angiogenic effect in a warm-blooded animal. Thus, reacting II (preparation given) with 1-[(isocyanophenylmethyl)sulfonyl]-4-methylbenzene in the presence of piperazine/THF for 6 days gave the thieno[2,3-d]pyrimidine III in 48% yield. In a cellular assay, II inhibited autophosphorylation of the Tie2 receptor with an IC₅₀ value of 2.2 μM. I are angiogenesis inhibitors for treating neoplasm (no data).

L14 ANSWER 4 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:300693 HCPLUS
DOCUMENT NUMBER: 134:311235

TITLE: Preparation of benzodiazepine derivatives as
 metabotropic glutamate receptor antagonists
 INVENTOR(S): Adam, Geo; Alanine, Alexander; Goetschi, Erwin; Mutel,
 Vincent; Woltering, Thomas Johannes
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
 SOURCE: PCT Int. Appl., 142 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029012	A2	20010426	WO 2000-EP9554	20000929
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2386980	AA	20010426	CA 2000-2386980	20000929
BR 2000014761	A	20020702	BR 2000-14761	20000929
EP 1224175	A2	20020724	EP 2000-971302	20000929
EP 1224175	B1	20040317		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200201026	T2	20020821	TR 2002-1026	20000929
JP 2003512360	T2	20030402	JP 2001-531812	20000929
AT 261945	E	20040415	AT 2000-971302	20000929
NZ 518037	A	20040430	NZ 2000-518037	20000929
PT 1224175	T	20040730	PT 2000-971302	20000929
ES 2215738	T3	20041016	ES 2000-971302	20000929
AU 779874	B2	20050217	AU 2001-10204	20000929
RU 2257382	C2	20050727	RU 2002-110107	20000929
US 6509328	B1	20030121	US 2000-687241	20001013
HR 20020260	B1	20041231	HR 2002-260	20020327
ZA 2002002654	A	20030704	ZA 2002-2654	20020404
NO 2002001691	A	20020410	NO 2002-1691	20020410
US 2003092677	A1	20030515	US 2002-300449	20021120
US 6960578	B2	20051101		
HK 1051037	A1	20050722	HK 2003-102801	20030417
US 2005234048	A1	20051020	US 2005-146693	20050607
US 7018998	B2	20060328		
US 2006148791	A1	20060706	US 2006-363351	20060227
PRIORITY APPLN. INFO.:			EP 1999-120519	A 19991015
			WO 2000-EP9554	W 20000929
			US 2000-687241	A3 20001013
			US 2002-300449	A3 20021120
			US 2005-146693	A1 20050607

OTHER SOURCE(S): MARPAT 134:311235
 GI



AB The title compds. [I; X is a single bond or an ethynediyl group; wherein, in case X is a single bond, R1 is hydrogen, halogen, nitro, lower alkyl, halo-lower alkyl, alkoxy carbonyl, lower cycloalkyl optionally substituted with oxygen, (un)substituted benzoyl or Ph, styrenyl, phenylethyl, naphthyl, biphenyl, benzofuranyl, or (un)substituted 5 or 6 membered heterocyclic ring; wherein in case X is an ethynediyl group, R1 is hydrogen, lower alkyl, optionally substituted with hydroxy, halo-lower alkyl, (un)substituted lower cycloalkyl or lower cycloalkenyl, lower alkenyl, (un)substituted Ph or 5 or 6 membered heterocyclic ring, or benzofuranyl; R3 is (un)substituted Ph, pyridinyl, thiophenyl, thiazolyl, or a 5-membered aromatic heterocycle, with the proviso that, if X is a single bond and R3 is pyridinyl, R1 is not hydrogen, or methyl] and their pharmaceutically acceptable acid addition salts are prepared. These compds. can be used for treating or preventing acute and/or chronic neurol. disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, and memory deficits. Thus, [2-amino-4-(4-fluorophenylethynyl)phenyl]-carbamic acid tert-Bu ester (preparation given) and 6-(3-imidazol-1-ylphenyl)-2,2-dimethyl-[1,3]dioxin-4-one (preparation given) were refluxed in toluene to give [4-(4-fluorophenylethynyl)-2-[3-(3-imidazol-1-ylphenyl)-3-oxopropionylamino]phenyl]carbamic acid tert-Bu ester which was treated with CF₃CO₂H in CH₂Cl₂ to give 8-(4-Fluorophenylethynyl)-4-(3-imidazol-1-ylphenyl)-1,3-dihydrobenzo[b](1,4)diazepin-2-one (II). II showed the antagonism against group II mGlu receptor with Ki of 0.004 μM in an assay using [³H]-LY354740 binding on mGlu2 transfected CHO cell membranes.

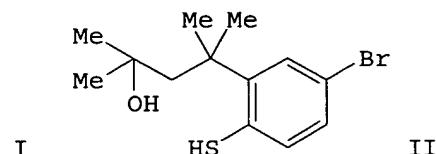
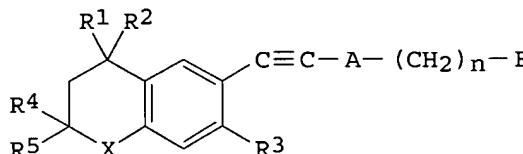
L14 ANSWER 5 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:490152 HCPLUS
 DOCUMENT NUMBER: 117:90152
 TITLE: Preparation of [(thio)chromanylethynyl]pyridines having retinoid-like activity
 INVENTOR(S): Chandraratna, Roshantha A. S.
 PATENT ASSIGNEE(S): Allergan, Inc., USA
 SOURCE: PCT Int. Appl., 70 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9206092	A1	19920416	WO 1991-US6900	19910924
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2091763	AA	19920410	CA 1991-2091763	19910924
AU 9186149	A1	19920428	AU 1991-86149	19910924

AU 657100	B2	19950302		
EP 555235	A1	19930818	EP 1991-917319	19910924
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 63412	A2	19930830	HU 1993-1031	19910924
JP 06501684	T2	19940224	JP 1991-515926	19910924
PL 168075	B1	19951230	PL 1991-299062	19910924
ZA 9108025	A	19920624	ZA 1991-8025	19911008
NO 9301343	A	19930604	NO 1993-1343	19930407
PRIORITY APPLN. INFO.:			US 1990-595128	A 19901009
OTHER SOURCE(S):			WO 1991-US6900	A 19910924
GI				

OTHER SOURCE(S): MARPAT 117:90152
GI



AB The title compds. [I; R₁-R₃ = H, alkyl; R₄, R₅ = H, alkyl, with provisos; A = pyridinyl, thieryl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl; B = H, (un)derivatized CO₂H, -CH₂OH, -CHO, -COR₆; R₆ = (cyclo)alkyl, alkenyl; n = 0-5] having retinoid-like activity (no data), useful for treating acne, psoriasis, eczema, lupus erythematosus, dry eye syndrome, etc., and in promoting wound healing and reversing the effects of sun damage to the skin, were prepared Esterification of 4-BrC₆H₄SH by Me₂C:CHCOCl gave 4-BrC₆H₄SCOCH:CCMe₂ which was cyclized by AlCl₃ in CH₂Cl₂ at room temperature to give 4,4-dimethyl-6-bromo-2-oxothiochroman. The ring cleavage-methylation of the latter by LiClO₄ and MeMgBr gave (hydroxybutyl)thiophenol (II) which was recyclized by refluxing with aqueous H₂SO₄. The resulting 2,2,4,4-tetramethyl-6-bromothiochroman was ethynylated by Me₃SiC.tplbond.CH, the protective group removed by KOH in Me₂CHOH, and the product thiochromanylacetylene coupled with Et 6-chloronicotinate to give title compound [I; R₁ = R₂ = R₄ = R₅ = Me, R₃ = H, A(CH₂)_nB = 3-ethoxycarbonylpyrid-6-yl].

L14 ANSWER 6 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1954:64065 HCPLUS
 DOCUMENT NUMBER: 48:64065
 ORIGINAL REFERENCE NO.: 48:11300e-i,11301a-i
 TITLE: Substituted acetylenes. LIX. Reactions of acetylenic primary amines
 AUTHOR(S): Hennion, G. F.; Teach, Eugene G.
 CORPORATE SOURCE: Univ. of Notre Dame, Notre Dame, IN
 SOURCE: Journal of the American Chemical Society (1953), 75, 4297-300
 CODEN: JACSAT; ISSN: 0002-7863
 DOCUMENT TYPE: Journal
 LANGUAGE: Unavailable
 OTHER SOURCE(S): CASREACT 48:64065
 AB cf. C.A. 48, 4431h. EtMeC(NH₂)C.tplbond.CH (I) undergoes transformations typical of the NH₂ group, the ethynyl H and the C.tplbond.C triple bond. The alkylation, acylation, hydrogenation, and addition to CO derivs. proceeded in the expected manner with good yields in nearly all

cases. I (48.5 g.), prepared as previously described (loc. cit.), treated with cold dilute (1:9) HCl to a faintly acidic reaction, 44.5 g. KOCH in 200 cc. H₂O added in 1 portion, and the mixture heated 4 hrs. on the steam bath and let stand overnight deposited 67.8 g. (96%) EtMeC(NHCONH₂)C.tplbond.CH, m. 101-3°; (recrystd. twice from EtOH, m. 103-5°). I (97 g.) added slowly to 200 g. p-MeC₆H₄SO₃Et (II), the mixture heated to 110° (where an exothermic reaction began), let stand 4 hrs. without heating, heated again 2 hrs. at 120-30°, let stand overnight, treated with 75 g. NaOH in 300 cc. H₂O, extracted with two 100-cc. portions of Et₂O, and the extract dried with MgSO₄ and K₂CO₃ and distilled gave 59.5 g. product, b₁₂₀ 74-82°, n_{25D} 1.4390-1.4310, which on redistn. yielded 42, g. (35%) EtMeC(NHEt)C.tplbond.CH, b₁₂₀ 77-8°, n_{25D} 1.4318, d₂₅ 0.802, giving with ammoniacal AgNO₃ a copious white precipitate I (97 g.) added to 200 g. II in 250 cc. C₆H₆, the solution

refluxed 2 hrs., cooled, treated with vigorous stirring with 50 g. NaOH in 400 cc. H₂O, the aqueous layer extracted with 50 cc. C₆H₆, the combined C₆H₆ layer

and extract dried with K₂CO₃, filtered, treated with 200 g. II, and the solution

refluxed 6 hrs., cooled overnight, treated with 50 g. KOH in 400 cc. H₂O, dried, and distilled gave 63.5 g. product, b₁₂₀ 99-103.5°, n_{25D} 1.4369-1.4397, which yielded on redistn. 56.5 g. (37%)

EtMeC(NEt₂)C.tplbond.CH (III), b₁₂₀ 103-5°, n_{25D} 1.4397, d₂₅ 0.812, giving a strongly pos. ammoniacal AgNO₃ test. III (31.6 g.) in 100 cc. MeOH hydrogenated 7 hrs. at 60 lb. pressure over 3-5 g. Raney Ni, the mixture filtered, the filtrate treated with 50 cc. 1:1 dilute HCl, distilled,

and

the 1st 50 cc. of distillate, b. 47-8°, treated with ice water, the organic layer washed, dried, distilled, and the distillate (10 g.), b. 64-8°, n_{25D} 1.3820-1.3870, redistd. from Na gave a fraction, b. 85-8°, n_{25D} 1.3810-1.3860, which was washed with four 5-cc. portions concentrated H₂SO₄, H₂O, and 10% aqueous Na₂CO₃ to give 3.6 g.

Et₂CHMe, b.

62-3.5°, n_{25D} 1.3738-1.3740; the original MeOH solution distilled to near dryness, the residue treated with 30 g. 50% NaOH, and the precipitated oil layer

dried with KOH pellets and distilled gave 3.7 g. Et₂NH, b. 55-6°, n_{25D} 1.3835 (identified as the p-toluenesulfonamide, m. 59-60°), and 4.2 g. distillate, b₃₀ 79-81°, n_{25D} 1.4343, which on redistn. gave 2.9 g. Et₂C(NEt)₂Me, b₃₀ 79-80°, n_{25D} 1.4350. I (18.4 g.) in 95 cc. 95% EtOH hydrogenated 1 hr. at 60 lb. initial pressure over 3-5 g. Raney Ni, the mixture treated with 20.4 g. I, treated again at 60 lb. H pressure, the catalyst filtered off, the filtrate acidified with 50 cc. concentrated HCl, the EtOH and H₂O distilled off in vacuo, the crystallized residue dissolved in

25

cc. H₂O, the solution treated with cooling with 50 cc. 40% NaOH, the amine layer taken up in Et₂O, and the Et₂O solution dried with K₂CO₃ and distilled gave 24.4 g. product, b. 100-7°, n_{25D} 1.4089-1.4115, which yielded on redistn. 20.2 g. (50%) Et₂MeCNH₂ (IV), b. 108-9°, n_{25D} 1.4115, d₂₅ 0.759. I (65 g.) in 200 cc. Et₂O added dropwise with stirring during 2 hrs. to 46 g. Na dissolved in 2 l. liquid NH₃, the mixture stirred 2.5 hrs., treated cautiously with 110 g. NH₄Cl in small portions, diluted with 500 cc. liquid NH₃ and 500 cc. Et₂O, let stand overnight, diluted with 300 cc. Et₂O and 300 cc. H₂O, the aqueous layer extracted with 100 cc. Et₂O, and

the

combined Et₂O layer and extract dried with K₂CO₃ and distilled gave 41 g. product, b. 103-4°, n_{25D} 1.4252-1.4281, which yielded on redistn. 29.5 g. (45%) EtMeC(NH₂)CH:CH₂ (V), b. 103-4°, n_{25D} 1.4250-1.4260, d₂₅ 0.782. V (9.9 g.) in 50 cc. EtOH hydrogenated with Raney Ni, the

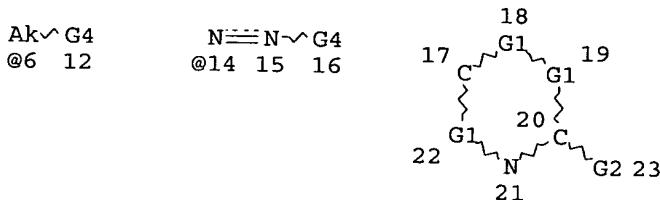
product taken up in C₆H₆, and the solution dried with MgSO₄, treated with 11.6 g. BzCl and 5 cc. pyridine, and worked up in the usual manner gave 15.3 g. Et₂MeCNHBz, m. 70-2° (recrystd. from light petr. ether, m. 73-4°). I (9.7 g.) and 10 cc. CS₂ in 50 cc. EtOH refluxed 4 hrs., the excess CS₂ and EtOH distilled off, the residue cooled, and the resulting pale yellow solid (17 g.) recrystd. from cyclohexane and light petr. ether yielded 15 g. 4-methyl-4-ethyl-5-methylene-2-thiazolidinethione, colorless crystals, m. 96-8° (recrystd. from C₆H₆-petr. ether, m. 97-8°). I (70 g.) in 100 cc. dry Et₂O added dropwise with stirring to NaNH₂ prepared from 16.5 g. Na in liquid NH₃, the mixture stirred 0.5 hr., treated during 45 min. slowly with 120 g. EtBr in 100 cc. anhydrous Et₂O, stirred 0.5 hr., let stand overnight to evaporate

most of the NH₃, diluted with 150 g. crushed ice, the aqueous layer extracted with

50 cc. Et₂O, and the combined Et₂O layer and extract dried with K₂CO₃ and distilled yielded 64 g. product, b₁₂₀ 94-8°, n_{25D} 1.4460-4435, which yielded on redistn. 54 g. (62%) EtMeC(NH₂)C.tplbond.CEt (VI), b₁₂₀ 98-9°, n_{25D} 1.4438, d₂₅ 0.812, λ_{maximum} 3.00, 3.08, 6.30 μ, giving a neg. AgNO₃ test. I (47.5 g.) treated similarly with NaNH₂ (from 12 g. Na) and 68.5 g. BuBr gave 53 g. product, b₂₅ 85-91°, n_{25D} 1.4490-1.4465, which yielded on redistn. 44 g. (59%) EtMeC(NH₂)C.tplbond.CBu, b₂₅ 92-3°, n_{25D} 1.4470, d₂₅ 0.810. VI (37.5 g.) in EtOH hydrogenated over Raney Ni gave 35 g. product, b₁₂₀ 92-7°, n_{25D} 1.4235-1.4242, which yielded on redistn. 29.5 g. (76%) EtMeC(NH₂)Bu, b₁₂₀ 86-7°, n_{25D} 1.4233, d₂₅ 0.776. VI (5 g.) heated with 5 cc. CS₂ yielded 7.5 g. 4-methyl-4-ethyl-5-propylidene-2-thiazolidinethione, pale yellow solid, m. 56-8°; recrystd. twice from petr. ether, colorless crystals, m. 59-60°. I (32.3 g.) added dropwise with stirring to NaNH₂ in liquid NH₃ from 7.6 g. Na, the mixture treated with 19.5 g. Me₂CO, stirred 2 hrs., let stand overnight to evaporate the NH₃, diluted with crushed ice and Et₂O, the Et₂O layer dried, evaporated, and the residue recrystd. twice from CCl₄-petr. ether gave 31 g. EtMeC(NH₂)C.tplbond.CC(OH)Me₂ (VII), white waxy crystals, m. 70-2°. I (32.3 g.) and 67 g. Ph₂CO gave similarly with NaNH₂ from 7.6 g. Na, 75 g. (76%) EtMeC(NH₂)C.tplbond.CC(OH)Ph₂ (VIII), m. 108-9°. VIII (5.6 g.) neutralized with the required amount of H₂SO₄ in 30 cc. Me₂CO gave VIII. 0.5H₂SO₄, m. 198° (decomposition) (from EtOH). VIII (14 g.) in 200 cc. EtOH hydrogenated 12 hrs. at 60 lb. initial pressure over 3 g. Raney Ni yielded 12.7 g. (89%) EtMeC(NH₂)CH₂CH₂C(OH)Ph₂, m. 85-9° (recrystd. twice from petr. ether, m. 94-5°). VII (6 g.) heated 4 hrs. with 5 cc. CS₂ in 30 cc. EtOH gave 7.6 g. 4-methyl-4-ethyl-5-(2-methyl-2-hydroxypropylidene)-2-thiazolidinethione (IX), m. 168-70°; recrystd. twice from EtOH, it m. 173-4° (decomposition). VIII (9.3 g.) and 5 cc. CS₂ in 50 cc. EtOH gave similarly 9.2 g. 5-(2,2-diphenyl-2-hydroxyethylidene) analog of IX, m. 156-8°; recrystd. twice from C₆H₆-petr. ether, it m. 163-4° (decomposition). EtMeC(NHBz)C.tplbond.CH (6.5 g.) in 20 cc. EtOH added slowly to 0.3 g. HgSO₄, 1 cc. H₂SO₄, 10 cc. H₂O, and 40 cc. EtOH at 60-70°, the mixture let stand at 60-70° 0.5 hr., cooled, filtered, evaporated, and the resulting product recrystd. from aqueous EtOH gave 2.7 g. EtMeC(NHBz)Ac, m. 85-7° (recrystd., it m. 87-8°).

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L2          SEL  PLU=ON  L1 1- CHEM :      2 TERMS
L3          46 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
L4          46 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 OR MTEP
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"BLADDER, DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7 148785 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR URINARY? OR ?CYSTITIS?
OR URINE(2A) LEAK? OR ENURESIS OR BED(W) WETTING
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L9 45 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 NOT L8
L15 7 SEA FILE=REGISTRY ABB=ON PLU=ON (168560-79-0/B1 OR 198419-91-
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VAR G2=6/14

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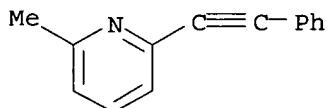
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GLUTAMATE(L) RECEPTOR
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OR TOLTERODINE OR DARIFENACIN OR TEMIVERINE
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L25 39 SEA FILE=REGISTRY ABB=ON PLU=ON L24 OR PRAZOSIN OR DOXAZOSIN
OR TERAZOSIN OR ALFUZOSIN OR TAMSULOSIN
L26 1150 SEA FILE=HCAPLUS ABB=ON PLU=ON L22 OR MGLU5 OR MGLUR5 OR
METABOTROPIC(W)GULTAMATE
L27 2191 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 OR ?ANTIMUSCARIN? OR
?OXYBUTYNIN? OR ?TOLTERODIN? OR ?DARIFENACIN? OR ?TEMIVERIN?
L28 16238 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 OR ADRENERGIC(W)ANTAG? OR
?PRAZOSIN? OR ?DOXAZOSIN? OR ?TERAZOSIN? OR ?ALFUZOSIN? OR
?TAMSULOSIN?
L31 19844 SEA FILE=HCAPLUS ABB=ON PLU=ON NEUROMUSCULAR?/CV OR NEUROMUSC
UL?
L32 0 SEA FILE=HCAPLUS ABB=ON PLU=ON (L18 AND (L27 OR L28 OR L31))
NOT (L8 OR L9)
L33 78 SEA FILE=HCAPLUS ABB=ON PLU=ON L18 (L)L26
L34 51 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND (?DRUG? OR ?MEDICIN?
OR ?PHARM? OR ?THERAP?)
L35 39 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 NOT (L8 OR L9)
L36 39 SEA FILE=HCAPLUS ABB=ON PLU=ON L32 OR L35

=> d ibib abs hitstr l36 1-39

L36 ANSWER 1 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:385171 HCPLUS
 DOCUMENT NUMBER: 144:445591
 TITLE: The effect of mGlu5 receptor positive allosteric modulators on signaling molecules in brain slices
 AUTHOR(S): Liu, Feng; Zhang, Guoming; Hornby, Geoffrey; Vasylyev, Dmytro; Bowlby, Mark; Park, Kaapjoo; Gilbert, Adam; Marquis, Karen; Andree, Terrance H.
 CORPORATE SOURCE: Wyeth Neuroscience Discovery Research, Princeton, NJ, 08543, USA
 SOURCE: European Journal of Pharmacology (2006), 536(3), 262-268
 CODEN: EJPHAZ; ISSN: 0014-2999
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Pos. allosteric modulators of metabotropic glutamate receptor subtype 5 (mGlu5) have promising therapeutic potential. The effects of selective mGlu5 receptor pos. allosteric modulators on signaling mols. in brain slices have not been previously reported. The current study demonstrated that the selective mGlu5 receptor pos. allosteric modulator, N-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2yl)-methyl]phenyl}-2-hydrobenzamide (CPPHA) potentiated the response to a subthreshold concentration of 3,5-dihydroxy-phenylglycine (DHPG) on extracellular signal-regulated protein kinase (ERK) and cyclic-AMP responsive element-binding protein (CREB) activity, as well as N-Me -aspartate (NMDA) receptor subunit NR1 phosphorylation in cortical and hippocampal slices. These results suggest that allosteric modulators of mGlu5 receptor could have physiol. significant effects by potentiating the actions of glutamate.
 IT 96206-92-7, MPEP
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (effect of mGlu5 pos. allosteric modulators on ERK1/2 and CREB signaling mols. in brain slices)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethyynyl)- (9CI) (CA INDEX NAME)



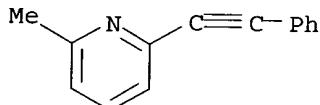
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 2 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:377142 HCPLUS
 DOCUMENT NUMBER: 145:43577
 TITLE: Differential roles for group 1 mGluR subtypes in induction and expression of chemically induced hippocampal long-term depression
 AUTHOR(S): Volk, Lenora J.; Daly, Christine A.; Huber, Kimberly M.
 CORPORATE SOURCE: Center for Basic Neuroscience, Department of Physiology, University of Texas Southwestern Medical Center, Dallas, TX, USA
 SOURCE: Journal of Neurophysiology (2006), 95(4), 2427-2438
 CODEN: JONEA4; ISSN: 0022-3077

PUBLISHER: American Physiological Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Although metabotropic glutamate receptors (mGluRs) mGluR1 and mGluR5 are often found to have similar functions, there is considerable evidence that the two receptors also serve distinct functions in neurons. In hippocampal area CA1, mGluR5 has been most strongly implicated in long-term synaptic depression (LTD), whereas mGluR1 has been thought to have little or no role. Here we show that simultaneous pharmacological blockade of mGluR1 and mGluR5 is required to block induction of LTD by the group 1 mGluR agonist, (RS)-3,5-dihydroxyphenylglycine (DHPG). Blockade of mGluR1 or mGluR5 alone has no effect on LTD induction, suggesting that activation of either receptor can fully induce LTD. Consistent with this conclusion, mGluR1 and mGluR5 both contribute to activation of extracellular signal-regulated kinase (ERK), which has previously been shown to be required for LTD induction. In contrast, selective blockade of mGluR1, but not mGluR5, reduces the expression of LTD and the associated decreases in AMPA surface expression. LTD is also reduced in mGluR1 knockout mice confirming the involvement of mGluR1. This shows a novel role for mGluR1 in long-term synaptic plasticity in CA1 pyramidal neurons. In contrast to DHPG-induced LTD, synaptically induced LTD with paired-pulse low-frequency stimulation persists in the pharmacological blockade of group 1 mGluRs and in mGluR1 or mGluR5 knockout mice. This suggests different receptors and/or upstream mechanisms for chemical and synaptically induced LTD.

IT 96206-92-7, MPEP
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (combined inhibition of mGluR1 by LY367385 and mGluR5 by MPEP
 was necessary to block DHPG-induced LTD and inhibited ERK
 phosphorylation, suggest different receptors and upstream mechanisms
 for chemical and synaptically induced LTD in mouse)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:1287400 HCAPLUS
 DOCUMENT NUMBER: 144:81038
 TITLE: A close structural analog of 2-methyl-6-(phenylethynyl)pyridine acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators
 AUTHOR(S): Rodriguez, Alice L.; Nong, Yi; Sekaran, Nishant K.; Alagille, David; Tamagnan, Gilles D.; Conn, P. Jeffrey
 CORPORATE SOURCE: Department of Pharmacology and Program in Translational Neuropharmacology, Vanderbilt University Medical Center, Nashville, TN, USA
 SOURCE: Molecular Pharmacology (2005), 68(6), 1793-1802
 PUBLISHER: American Society for Pharmacology and Experimental

Therapeutics

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB The metabotropic glutamate receptor subtype 5 (mGlu5) activates calcium mobilization via binding of glutamate, the major excitatory neurotransmitter in the central nervous system. Allosteric modulation of the receptor has recently emerged as a promising alternative method of regulation to traditional regulation through orthosteric ligands. We now report three novel compds. that bind to the allosteric 2-methyl-6-(phenylethynyl)-pyridine (MPEP) site on mGlu5 but have only partial inhibition or no functional effects on the mGlu5 response. Two of these compds., 2-(2-(3-methoxyphenyl)ethynyl)-5-methylpyridine (M-5MPEP) and 2-(2-(5-bromopyridin-3-yl)ethynyl)-5-methylpyridine (Br-5MPEPy), act as partial antagonists of mGlu5 in that they only partially inhibit the response of this receptor to glutamate. The third compound, 5-methyl-6-(phenylethynyl)-pyridine (5MPEP), acts as a neutral allosteric site ligand that binds to the MPEP site and has no effects alone. However, 5MPEP blocks the effects of both the allosteric antagonist MPEP and potentiatos 3,3'-difluorobenzaldazine and 3-cyanol-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB). This compound also blocks depolarization effects of both MPEP and CDPPB in neurons in the subthalamic nucleus. These novel compds. provide valuable new insight into the pharmacol. of allosteric sites on G protein-coupled receptors and provide valuable new tools for determining the effects of allosteric site ligands in native systems.

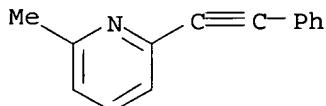
IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)

(MPEP analog acts as neutral allosteric site ligand on mGlu5 and blocks multiple allosteric modulators)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1264567 HCPLUS

DOCUMENT NUMBER: 144:121572

TITLE: The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice

AUTHOR(S): Hodge, Clyde W.; Miles, Michael F.; Sharko, Amanda C.; Stevenson, Rebekah A.; Hillmann, Jennie R.; Lepoutre, Veronique; Besheer, Joyce; Schroeder, Jason P.

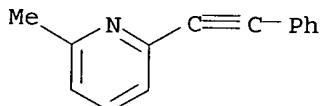
CORPORATE SOURCE: Department of Psychiatry, Bowles Center for Alcohol Studies School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7178, USA

SOURCE: Psychopharmacology (Berlin, Germany) (2006), 183(4), 429-438

CODEN: PSCHDL; ISSN: 0033-3158

PUBLISHER: Springer GmbH

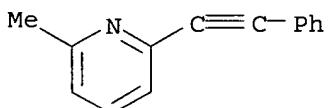
DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Many of the biochem., physiol., and behavioral effects of ethanol are known to be mediated by ionotropic glutamate receptors. Emerging evidence implicates metabotropic glutamate receptors (mGluRs) in the biobehavioral effects of ethanol and other drugs of abuse, but there is little information regarding the role of mGluRs in the reinforcing effects of ethanol. Male C57BL/6J mice were trained to lever-press on a concurrent fixed ratio 1 schedule of ethanol (10% volume/volume) vs. water reinforcement during 16-h sessions. Effects of mGluR1, mGluR2/3, and mGluR5 antagonists were then tested on parameters of ethanol self-administration behavior. The mGluR5 antagonist MPEP (1 - 10 mg/kg, i.p.) dose-dependently reduced ethanol-reinforced responding but had no effect on concurrent water-reinforced responding. Anal. of the temporal pattern of responding showed that MPEP reduced ethanol-reinforced responding during peak periods of behavior occurring during the early hours of the dark cycle. Further anal. showed that MPEP reduced the number of ethanol response bouts and bout-response rate. MPEP also produced a 13-fold delay in ethanol response onset (i.e., latency to the first response) with no corresponding effect on water response latency or locomotor activity. The mGluR1 antagonist CPCCOEt (1 - 10 mg/kg, i.p.) or the mGluR2/3 antagonist LY 341495 (1 - 30 mg/kg, i.p.) failed to alter ethanol- or water-reinforced responding. These data indicate that mGlu5 receptors selectively regulate the onset and maintenance of ethanol self-administration in a manner that is consistent with reduction in ethanol's reinforcement function.
 IT 96206-92-7, MPEP
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethyynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:1182409 HCAPLUS
 DOCUMENT NUMBER: 143:399661
 TITLE: Fenobam: A clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity
 AUTHOR(S): Porter, Richard H. P.; Jaeschke, Georg; Spooren, Will; Ballard, Theresa M.; Buttelmann, Bernd; Kolczewski, Sabine; Peters, Jens-Uwe; Prinseen, Eric; Wichmann, Jurgen; Vieira, Eric; Muhlemann, Andreas; Gatti, Silvia; Mutel, Vincent; Malherbe, Pari
 CORPORATE SOURCE: Pharma Division, Discovery Research CNS, F. Hoffmann-La Roche, Basel, Switz.
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 315(2), 711-721
 CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fenobam [N-(3-chlorophenyl)-N'-(4,5-dihydro-1-methyl-4-oxo-1H-imidazole-2-yl)urea] is an atypical anxiolytic agent with unknown mol. target that has previously been demonstrated both in rodents and human to exert anxiolytic activity. Here, we report that fenobam is a selective and potent metabotropic glutamate (mGlu)5 receptor antagonist acting at an allosteric modulatory site shared with 2-methyl-6-phenylethynyl-pyridine (MPEP), the prototypical selective mGlu5 receptor antagonist. Fenobam inhibited quisqualate-evoked intracellular calcium response mediated by human mGlu5 receptor with IC₅₀ = 58±2 nM. It acted in a noncompetitive manner, similar to MPEP and demonstrated inverse agonist properties, blocking 66% of the mGlu5 receptor basal activity (in an over expressed cell line) with an IC₅₀ = 84±13 nM. [3H]Fenobam bound to rat and human recombinant receptors with K_d values of 54±6 and 31±4 nM, resp. MPEP inhibited [3H]fenobam binding to human mGlu5 receptors with a K_i value of 6.7±0.7 nM, indicating a common binding site shared by both allosteric antagonists. Fenobam exhibits anxiolytic activity in the stress-induced hyperthermia model, Vogel conflict test, Geller-Seifter conflict test, and conditioned emotional response with a min. ED of 10 to 30 mg/kg p.o. Furthermore, fenobam is devoid of GABAergic activity, confirming previous reports that fenobam acts by a mechanism distinct from benzodiazepines. The non-GABAergic activity of fenobam, coupled with its robust anxiolytic activity and reported efficacy in human in a double blind placebo-controlled trial, supports the potential of developing mGlu5 receptor antagonists with an improved therapeutic window over benzodiazepines as novel anxiolytic agents.
IT 96206-92-7, MPEP
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonbenzodiazepine anxiolytic fenobam is mGlu5 receptor antagonist with inverse agonist activity)
RN 96206-92-7 HCPLUS
CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 6 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1175525 HCPLUS
DOCUMENT NUMBER: 144:230817
TITLE: Role of peripheral group I and II metabotropic glutamate receptors in IL-1 β -induced mechanical allodynia in the orofacial area of conscious rats
AUTHOR(S): Ahn, Dong K.; Kim, Kwang H.; Jung, Chang Y.; Choi, Hyo S.; Lim, Eun J.; Youn, Dong H.; Bae, Yong C.
CORPORATE SOURCE: Department of Oral Physiology and Neurobiology, School of Dentistry, Kyungpook National University, 188-1 Sam Deok 2 ga, Chung-gu, Taegu, 700 412, S. Korea
SOURCE: Pain (2005), 118(1-2), 53-60
CODEN: PAINDB; ISSN: 0304-3959

PUBLISHER: Elsevier Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The present study investigated the role of peripheral group I and II metabotropic glutamate receptors (mGluRs) in interleukin-1 β (IL-1 β)-induced mech. allodynia in the orofacial area. Expts. were carried out on Sprague-Dawley rats weighing between 230 and 280 g. After s.c. administration of 0.01, 0.1, 1, or 10 pg of IL-1 β , we examined withdrawal behavioral responses produced by 10 successive trials of a ramp of air-puffs pressure applied ipsilaterally or contralaterally to the IL-1 β injection site. The thresholds of air puffs were measured 10, 30, 60, 120, or 180 min after 25 μ l of IL-1 β was administered through an implanted tube. S.c. injection of IL-1 β produced bilateral mech. allodynia. While the IL-1 β -induced mech. allodynia was blocked by pretreatment with an IL-1 receptor antagonist, the IL-1 β -induced mirror-image mech. allodynia was not blocked by an IL-1 receptor antagonist injected into the contralateral side. S.c. administration of CPCCOEt or LY367385, an mGluR1 antagonist, or MPEP or SIB1893, an mGluR5 antagonist, 10 min prior to injection of IL-1 β abolished IL-1 β -induced mech. allodynia. Pretreatment with APDC or DCG4, a group II mGluR agonist, blocked the IL-1 β -induced mech. allodynia. The anti-allodynic effect induced by APDC was inhibited by pretreatment with LY341495, a group II mGluR antagonist. These results suggest that peripheral group I and II mGluRs participate in IL-1 β -induced mech. allodynia in the orofacial area. Peripheral group I mGluR antagonists blocked the IL-1 β -induced mech. allodynia, while peripheral group II mGluR agonists produced anti-allodynic effects on IL-1 β -induced mech. allodynia in the orofacial area of rats.

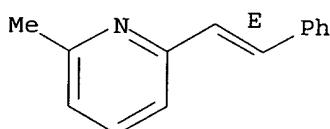
IT 7370-21-0, SIB1893

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (group I metabotropic glutamate receptor, mGluR5 antagonist,
 2-methyl-6-(2-phenylethenyl)pyridine blocked interleukin-1 β
 induced mech. allodynia in orofacial area of rat)

RN 7370-21-0 HCPLUS

CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

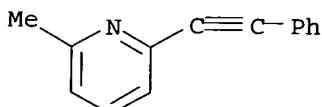


IT 96206-92-7, MPEP

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (group I metabotropic glutamate receptor, mGluR5 antagonist,
 2-methyl-6-(phenylethynyl)-pyridine hydrochloride blocked
 interleukin-1 β induced mech. allodynia in orofacial area of rat)

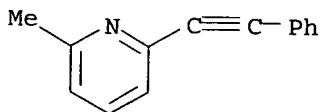
RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:761715 HCAPLUS
 DOCUMENT NUMBER: 143:279121
 TITLE: Metabotropic glutamate receptor (mGluR5) antagonist
 MPEP attenuated cue- and schedule-induced
 reinstatement of nicotine self-administration behavior
 in rats
 AUTHOR(S): Bespalov, Anton Y.; Dravolina, Olga A.; Sukhanov,
 Ilya; Zakharova, Elena; Blokhina, Elena; Zvartau,
 Edwin; Danysz, Wojciech; Van Heeke, Gino; Markou,
 Athina
 CORPORATE SOURCE: Institute of Pharmacology, Pavlov Medical University,
 St. Petersburg, Russia
 SOURCE: Neuropharmacology (2005), 49(Suppl. 1), 167-178
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Previous studies suggested that metabotropic glutamate 5 (mGlu5) receptors play an important role in the reinforcing effects of abused drugs. The present expts. evaluated the effects of the mGlu5 receptor antagonist, MPEP (2-methyl-6-(phenylethynyl)-pyridine hydrochloride; 1-10 mg/kg, salt, i.p.), in rat models of nicotine-seeking behavior that may have relevance to relapse to drug-taking. Male Wistar rats (with restricted access to food) were trained to nose-poke to receive i.v. infusions of nicotine (0.03 mg/kg per infusion, base) under a fixed ratio 5 time out 60 s schedule of reinforcement. After stable nicotine self-administration was acquired, nose-poking behavior was extinguished in the absence of nicotine-associated cues. During the reinstatement test phase, independent groups of animals were exposed to: (a) response-contingent nicotine-associated cues (cue-induced reinstatement); or (b) response-noncontingent presentations of 45-mg food pellets under fixed time 2 min schedule (schedule-induced reinstatement). Addnl. control expts. were conducted to demonstrate that in nicotine-naive animals MPEP does not affect cue-induced reinstatement of food-seeking behavior and has no effects on operant behavior maintained by a simple fixed interval 2 min schedule of food reinforcement. Pretreatment with MPEP (10 mg/kg) significantly attenuated the reinstatement of nicotine-seeking in both expts. Further, MPEP (10 mg/kg) significantly attenuated polydipsia induced by a fixed time 2 min food schedule. In conclusion, the present findings indicate that the blockade of mGlu5 receptors attenuates cue-induced reinstatement of nicotine self-administration behavior (but not food-seeking) and may produce a general inhibition of schedule-induced behaviors, including schedule-induced nicotine-seeking.
 IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist MPEP attenuated cue- and schedule-induced reinstatement of nicotine self-administration behavior in rats)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 8 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:309177 HCPLUS
 DOCUMENT NUMBER: 142:441731
 TITLE: Functional interaction between mGlu 5 and NMDA receptors in a rat model of Parkinson's disease
 AUTHOR(S): Turle-Lorenzo, Nathalie; Breysse, Nathalie; Baunez, Christelle; Amalric, Marianne
 CORPORATE SOURCE: CNRS and Universite de Provence, Marseille, Fr.
 SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 117-127
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English

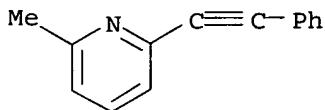
AB Electrophysiolog. evidence suggests a synergistic relationship between metabotropic (mGlu) and ionotropic (iGlu) glutamate receptors. The functional consequences of these interactions have not been investigated in neurodegenerative diseases such as in Parkinson's disease. The goals of this study are as follows: (1) to investigate the effects of 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and dizocilpine (MK-801), antagonists at metabotropic glutamate 5 (mGlu5) and NMDA receptors, resp., on the akinetic syndrome observed in bilateral 6-OHDA-lesioned rats; (2) to investigate if the effects of MPEP were potentiated by co-treatment with a behaviorally inactive dose of MK-801; and (3) to investigate the effects of L-DOPA alone and in combination with MPEP on the akinetic syndrome observed in 6-OHDA-lesioned rats. The effects of the different treatments (single and co-treatment) administered for 3 wk were measured in 6-OHDA-lesioned rats trained to release a lever rapidly after a visual stimulus onset in a simple reaction time task. MPEP 0.75 mg/kg reversed the akinetic deficits produced by striatal dopamine depletion, while MPEP 0.375 mg/kg had no effect. Co-administration with MK-801 0.02 mg/kg, ineffective alone, failed to speed the recovery process of MPEP 0.75 mg/kg but revealed the antiakinetic action of MPEP 0.375 mg/kg. L-DOPA 3 mg/kg alone had a potent antiakinetic effect in 6-OHDA lesioned rats, and this effect was not potentiated by a subthreshold MPEP treatment. These results support a critical role for mGlu5 receptor blockade in improving Parkinsonian symptomatology. either as a single treatment or in combination with low concns. of L-DOPA and demonstrate an interaction between NMDA and mGluR5 in regulating these effects.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mGluR5 receptor antagonist alone/combined with L-DOPA effect on NMDA and mGluR5 interaction in rat model of Parkinson's disease)

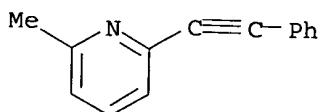
RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



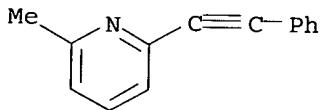
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 9 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:309160 HCPLUS
 DOCUMENT NUMBER: 142:456874
 TITLE: The metabotropic glutamate receptor 5 antagonist MPEP decreased break points for nicotine, cocaine, and food in rats
 AUTHOR(S): Paterson, Neil E.; Markou, Athina
 CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, 92037, USA
 SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 255-261
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The metabotropic glutamate (mGlu5) receptor subtype 5 antagonist MPEP attenuates self-administration of numerous drugs of abuse. The purpose of the present study was to explore whether MPEP-induced decreases in nicotine and cocaine self-administration reflect attenuation of the reinforcing and incentive motivational effects of nicotine and cocaine. The effects of MPEP on breaking points maintained by nicotine, cocaine, or feed were assessed using a progressive ratio schedule of reinforcement. Breaking points obtained under such schedules are postulated to reflect both the reinforcing and incentive motivational properties of reinforcers. Rats were allowed to respond for nicotine (0.05 mg/kg per infusion, free base), cocaine (0.18 mg/kg per infusion, salt), or feed (45 mg pellets) under a progressive ratio schedule of reinforcement. After establishing stable and equivalent levels of responding for all 3 reinforcers, rats underwent one test session where no rewards were presented to assess the effects of 1-day extinction, similar to 1-day pharmacol.-induced extinction, on performance in this schedule. Subsequently, rats were again allowed to respond for nicotine, cocaine, or feed until reestablishment of stable levels of responding. Then, MPEP (1-9 mg/kg) was administered i.p. according to a within-subjects Latin square design, 30 min prior to the testing sessions. Responding in the absence of a primary reinforcer was significantly decreased compared to responding under baseline conditions. Further, MPEP decreased break points maintained by nicotine, cocaine, and feed. The mGlu5 receptor is implicated in mediating the reinforcing and incentive motivational properties of nicotine, cocaine, and feed.
 IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist MPEP decreased break points for nicotine, cocaine, and feed in rats)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 10 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:243148 HCPLUS
 DOCUMENT NUMBER: 142:404093
 TITLE: Effect of MPEP, a selective mGluR5 antagonist, on the antielectroshock activity of conventional antiepileptic drugs
 AUTHOR(S): Zadrożniak, Marek; Sekowski, Andrzej; Czuczwarc, Stanisław J.; Borowicz, Kinga K.
 CORPORATE SOURCE: Department of Pathophysiology, Medical University, Lublin, PL 20-090, Pol.
 SOURCE: Polish Journal of Pharmacology (2004), 56(5), 595-598
 PUBLISHER: Polish Academy of Sciences, Institute of Pharmacology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB MPEP, a selective non-competitive antagonist of group I metabotropic glutamate receptor subtype 5 (mGluR5), administered at doses ranging from 0.75 to 1 mg/kg, failed to influence the electroconvulsive threshold in mice. However, when administered at higher doses (1.25 and 1.5 mg/kg), it significantly increased the threshold. Moreover, MPEP (applied at its highest subprotective dose of 1 mg/kg) did not affect the protective action of valproate, carbamazepine, diphenylhydantoin and phenobarbital against maximal electroshock-induced seizures in mice. The presented results indicate that mGluR5 antagonists should not be considered as good candidates for add-on therapy of generalized seizures.
 IT 96206-92-7, 2-Methyl-6-phenylethylnylpyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (selective non-competitive mGluR5 antagonist MPEP at high dose significantly increased electroconvulsive threshold and did not influence antiseizure efficacy of antiepileptic drugs in electroshock-induced seizure in mouse)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 11 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:225601 HCPLUS
 DOCUMENT NUMBER: 142:423627
 TITLE: SIB 1893, a selective mGluR5 receptor antagonist, potentiates the anticonvulsant activity of

oxcarbazepine against amygdala-kindled convulsions in rats

AUTHOR(S): Borowicz, Kinga K.; Luszczki, Jarogniew J.; Czuczwar, Stanislaw J.

CORPORATE SOURCE: Department of Pathophysiology, Skubiszewski Medical University, Lublin, PL 20-090, Pol.

SOURCE: Polish Journal of Pharmacology (2004), 56(4), 459-464
CODEN: PJPAE3; ISSN: 1230-6002

PUBLISHER: Polish Academy of Sciences, Institute of Pharmacology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB SIB 1893 (a non-competitive antagonist of group I metabotropic glutamate receptors), given at 40 mg/kg (but not at 20-30 mg/kg), shortened the afterdischarge duration in amygdala-kindled rats, being ineffective on other seizure parameters - seizure severity, seizure duration, and afterdischarge threshold. Oxcarbazepine (at 7.5 mg/kg, but not at 5 mg/kg), a newer antiepileptic drug, reduced seizure severity, seizure and afterdischarge durations. When combined at ineffective doses in amygdala kindling, SIB 1893 at 20 or 30 mg/kg and oxcarbazepine at 5 mg/kg, significantly reduced seizure and afterdischarge durations. The results indicate that combinations of oxcarbazepine with antagonists of group I metabotropic glutamate receptors may offer a novel therapeutic approach in cases of drug-resistant epilepsy.

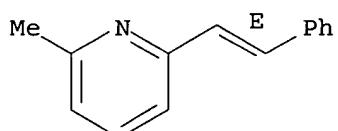
IT 7370-21-0, SIB 1893

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of selective mGluR5 receptor antagonist SIB 1893 at subprotective dose of 30 mg/kg with antiepileptic drug oxcarbazepine at 5 mg/kg significantly reduced seizure, afterdischarge duration in rat with amygdala-kindled convolution)

RN 7370-21-0 HCPLUS

CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 12 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:101814 HCPLUS

DOCUMENT NUMBER: 142:233126

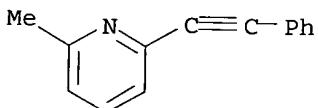
TITLE: The mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine decreases ethanol consumption via a protein kinase C ϵ -dependent mechanism

AUTHOR(S): Olive, M. Foster; Mcgeehan, Andrew J.; Kinder, Jennifer R.; McMahon, Thomas; Hodge, Clyde W.; Janak, Patricia H.; Messing, Robert O.

CORPORATE SOURCE: Ernest Gallo Clinic and Research Center, Department of Neurology, University of California at San Francisco, Emeryville, CA, USA

SOURCE: Molecular Pharmacology (2005), 67(2), 349-355
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Glutamatergic neurotransmission plays a critical role in addictive behaviors, and recent evidence indicates that genetic or pharmacological inactivation of the type 5 metabotropic glutamate receptor (mGluR5) reduces the self-administration of cocaine, nicotine, and alcohol. Radioligand binding experiments using [³H]MPEP revealed that these genotypic differences in response to MPEP were not a result of altered mGluR5 levels or binding in PKC ϵ -null mice. Our data indicate that mGluR5 is coupled to PKC ϵ via a PI3K-dependent pathway and that PKC ϵ is required for the ability of the mGluR5 antagonist MPEP to reduce ethanol consumption.
 IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist 6-Me-2-(phenylethynyl)pyridine decreases ethanol consumption via a protein kinase C ϵ -dependent mechanism)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



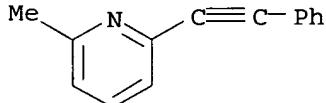
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 13 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:50048 HCPLUS
 DOCUMENT NUMBER: 142:290548
 TITLE: Role of γ -aminobutyric acid (GABA) and metabotropic glutamate receptors in nicotine reinforcement: potential pharmacotherapies for smoking cessation
 AUTHOR(S): Markou, Athina; Paterson, Neil E.; Semenova, Svetlana
 CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, 92037, USA
 SOURCE: Annals of the New York Academy of Sciences (2004), 1025 (Current Status of Drug Dependence/Abuse Studies), 491-503
 CODEN: ANYAA9; ISSN: 0077-8923
 PUBLISHER: New York Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Previous work indicated a role for GABA and glutamate in the reinforcing effects of drugs of abuse. The present studies assessed the effects of GABAergic and glutamatergic manipulations on the reinforcing effects of nicotine as assessed by i.v. nicotine self-administration. Male Wistar rats were allowed to self-administer either of two nicotine doses under a fixed ratio or a progressive ratio schedule of reinforcement. The effects of a glutamatergic compound on nicotine self-administration in male DBA/2J mice were also explored. Finally, to assess for nonspecific effects of the drug manipulations, the effects of all test compounds on responding maintained by a food reinforcer

were investigated. The pharmacol. manipulations used were: γ -vinyl-GABA (vigabatrin or GVG), an irreversible inhibitor of GABA transaminase, the GABAB receptor agonists (-)baclofen and CGP44532, and the metabotropic glutamate receptor 5 (mGluR5) antagonist MPEP. GVG, CGP44532, and (-)baclofen dose-dependently decreased nicotine self-administration on the fixed-ratio schedule, but also decreased food-maintained responding. Furthermore, CGP44532 decreased breakpoints for nicotine and food at identical doses under the progressive-ratio schedule. MPEP dose-dependently decreased nicotine self-administration with no effect on food-maintained responding in rats. MPEP also decreased nicotine self-administration in the mice. These results demonstrate that activation of GABAB receptors or blockade of mGluR5 decreased nicotine self-administration. Although there was some selectivity for the effects of the GABAergic manipulations, there was clear selectivity of the effects of MPEP on nicotine-vs. food-maintained responding. Thus, compds. that increase GABAergic neurotransmission and antagonists at mGluR5 have potential as antismoking medications for humans.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist MPEP dose-dependently increased glutamatergic transmission through mGluR5 blockade, decreased nicotine consumption under fixed-ratio schedule reinforcement with no effect on food-maintained responding in rat)

RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)

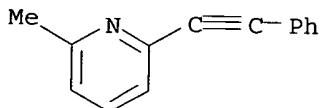


REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 14 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:807234 HCPLUS
 DOCUMENT NUMBER: 141:343335
 TITLE: The mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) potentiates PCP-induced cognitive deficits in rats
 AUTHOR(S): Campbell, Una C.; Lalwani, Kush; Hernandez, Lisa; Kinney, Gene G.; Conn, P. Jeffrey; Bristow, Linda J.
 CORPORATE SOURCE: Department of Pharmacology, Merck Research Laboratories, San Diego, CA, 92121, USA
 SOURCE: Psychopharmacology (Berlin, Germany) (2004), 175(3), 310-318
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Rationale: Recent studies have shown that metabotropic glutamate receptor 5 (mGluR5) can modulate N-methyl-D-aspartate (NMDA) receptor function in vivo. For example, the mGluR5 antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP) can potentiate PCP (phencyclidine)-evoked hyperactivity and PCP-induced disruptions in prepulse inhibition (PPI) in rats. Objective: To extend these previous behavioral findings and determine whether the mGluR5 antagonist MPEP can modulate the disruptions in

learning and memory induced by PCP in rats. Methods: The effects of MPEP, alone and in combination with PCP, were evaluated in rats trained to perform a repeated acquisition procedure (learning) or a delayed nonmatching to position (DNMTP) radial maze task (spatial memory). Results: In the repeated acquisition task, MPEP (0-10 mg/kg, IP) dose-dependently decreased response rates but had no effect on response accuracy. In contrast, PCP (0.625-1.25 mg/kg, SC) reduced response rate and response accuracy in a dose-dependent manner. Although MPEP (10 mg/kg, IP) had no effect when administered alone, the mGluR5 antagonist potentiated the disruptions in learning induced by a low dose of PCP (0.625 mg/kg, SC). In the DNMTP maze task, MPEP (0-10 mg/kg, IP) had no effect on spatial memory, whereas PCP (1.25-2.5 mg/kg, SC) produced a dose-dependent disruption. MPEP (10 mg/kg, IP) potentiated the impairments in memory induced by PCP (1.25 mg/kg, SC). Conclusion: The mGluR5 antagonist, MPEP, potentiated the disruptions in learning and memory induced by PCP. These behavioral data extend previous behavioral findings and further suggest that mGluR5 can modulate NMDA receptor function in vivo.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl) pyridine
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (mGluR5 antagonist 2-Me-6-(phenylethynyl)-pyridine (MPEP)
 potentiates PCP-induced cognitive deficits in rats)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



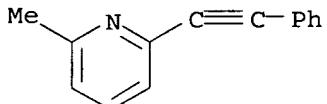
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:580035 HCAPLUS
 DOCUMENT NUMBER: 142:49023
 TITLE: Simultaneous Blockade of Adenosine A2A and Metabotropic Glutamate mGlu5 Receptors Increase their Efficacy in Reversing Parkinsonian Deficits in Rats
 Coccurello, Roberto; Breysse, Nathalie; Amalric, Marianne
 AUTHOR(S):
 CORPORATE SOURCE: Laboratoire de Neurobiologie de la Cognition, CNRS and Universite de Provence, Marseille, Fr.
 SOURCE: Neuropsychopharmacology (2004), 29(8), 1451-1461
 CODEN: NEROEW; ISSN: 0893-133X
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Recent evidence suggest that antagonism of adenosine A2A receptors represent an alternative therapeutic approach to Parkinson's disease (PD). Coactivation of A2A and the glutamate subtype 5 metabotropic receptors (mGlu5) synergistically stimulates DARPP-32 phosphorylation and c-fos expression in the striatum. This study therefore tested the effects of a joint blockade of these receptors to alleviate the motor dysfunction in a rat model of PD. 6-Hydroxydopamine infusions in the striatum produced akineti deficits in rats trained to release a lever after a stimulus in a reaction time (RT) task. At 2 wk after the lesion, A2A and mGlu5 receptors selective antagonists

8-(3-chlorostyryl)caffeine (CSC) and 2-methyl-6-(phenylethynyl)-pyridine (MPEP) were administered daily for 3 wk either as a single or joint treatment. Injections of CSC (1.25 mg/kg) and MPEP (1.5 mg/kg) sep. or in combination reduced the increase of delayed responses and RTs induced by 6-OHDA lesions, while the same treatment had no effect in controls. Furthermore, coadministration of lower doses of 0.625 mg/kg CSC and 0.375 mg/kg MPEP noneffective as a single treatment promoted a full and immediate recovery of akinesia, which was found to be more efficient than the sep. blockade of these receptors. These results demonstrate that the combined inactivation of A2A and mGlu5 receptor potentiate their beneficial effects supporting this pharmacol. strategy as a promising anti-Parkinsonian therapy.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGlu5 receptor antagonist, MPEP alone or in combination with CSC reversed akinetic deficits by reducing increased delayed responses and reaction time thus improving motor control in mouse model of PD)

RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)

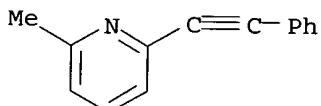


REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:471805 HCAPLUS
 DOCUMENT NUMBER: 141:47165
 TITLE: Effects of mGlu1 and mGlu5 metabotropic glutamate antagonists to reverse morphine tolerance in mice
 Smith, Forrest L.; Smith, Paul A.; Dewey, William L.; Javed, Ruby R.
 AUTHOR(S):
 CORPORATE SOURCE: Department of Pharmacology and Toxicology, Virginia Commonwealth University Medical Center, Richmond, VA, 23298-0613, USA
 SOURCE: European Journal of Pharmacology (2004), 492(2-3), 137-142
 CODEN: EJPHAZ; ISSN: 0014-2999
 PUBLISHER: Elsevier Science B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Intracerebroventricular (i.c.v.) injection of phospholipase C inhibitors and structurally dissimilar PKC inhibitors were shown to completely reverse morphine antinociceptive tolerance in mice. Since Group I metabotropic glutamate receptors (mGlu1 and mGlu5) activate phospholipase C through Gαq Gα11 proteins, we hypothesized that morphine tolerance could occur through an increase in mGlu1 and mGlu5 receptor stimulation. Seventy-two hours after implantation of placebo or 75 mg morphine pellets, mice were tested in the 56° warm-water tail-withdrawal test following i.c.v. injection of vehicle or test drug. The mGlu1 receptor antagonist CPCCOEt (7-(Hydroxyimino)cyclopropa[b]chromen-1a-carboxylate Et ester) partly but significantly reversed morphine tolerance. The mGlu5 receptor antagonist MPEP (2-Methyl-6-(phenylethynyl)pyridine hydrochloride) also partly

reversed the antinociceptive tolerance. Co-administering CPCCOEt with MPEP completely reversed the tolerance. Furthermore, the mixed mGlu1/mGlu5 antagonist AIDA ((RS)-1-Aminoindan-1,5-dicarboxylic acid) also completely reversed the tolerance. Thus, greater mGlu1 and mGlu5 receptor stimulation during morphine tolerance may lead to persistent activation of the phosphatidylinositol cascade.

IT 96206-92-7, MPEP
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (effects of mGlu1 and mGlu5 metabotropic glutamate antagonists to reverse morphine tolerance in mice)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



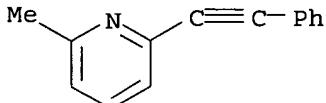
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:317555 HCAPLUS
 DOCUMENT NUMBER: 141:307385
 TITLE: mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior
 AUTHOR(S): Baeckstroem, Pia; Bachteler, Daniel; Koch, Sabrina; Hyytiae, Petri; Spanagel, Rainer
 CORPORATE SOURCE: National Public Health Institute, Helsinki, Finland
 SOURCE: Neuropsychopharmacology (2004), 29(5), 921-928
 CODEN: NEROEW; ISSN: 0893-133X
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The glutamatergic system plays an important role in mediating neurobehavioral effects of EtOH. Metabotropic glutamate receptors subtype 5 (mGluR5) are modulators of glutamatergic neurotransmission and are abundant in brain regions known to be involved in ethanol self-administration. Here, the authors studied the effects of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a highly potent, noncompetitive mGlu5 receptor antagonist, on voluntary EtOH consumption and relapse behavior. For this purpose, the authors used 2 models for the measurement of relapse behavior: (i) reinstatement of EtOH-seeking behavior by drug-associated cues and (ii) the alc. deprivation effect in long-term EtOH-consuming rats. In the 1st set of expts., rats were trained to lever press for EtOH in the presence of a distinct set of cues. After extinction, the animals were exposed to the resp. cues that initiated reinstatement of responding. A response-contingent EtOH prime further enhanced responding compared to the conditioned cues alone. Under these conditions, MPEP (0, 1, 3, and 10 mg/kg) attenuated EtOH seeking significantly and in a dose-related manner. However, at the highest dose, MPEP also decreased the number of inactive lever responses. In the 2nd set of expts., rats with 1 yr of EtOH experience and repeated deprivation phases were used. A subchronic treatment with MPEP (twice daily; 0, 3, and 10 mg/kg) resulted in a significant and dose-dependent reduction of the alc. deprivation effect (ADE). Although the same MPEP treatment regimen decreased baseline drinking, this effect was not as pronounced as on the

ADE. These results show in 2 commonly used models of relapse to EtOH that pharmacol. targeting of mGlu5 receptors may be a promising approach for the treatment of alcoholism.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonist MPEP reduces EtOH-seeking and relapse behavior)

RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:131734 HCAPLUS
 DOCUMENT NUMBER: 141:218748
 TITLE: In the Amygdala Anxiolytic Action of mGlu5 Receptors Antagonist MPEP Involves Neuropeptide Y but not GABA A Signaling
 AUTHOR(S): Wieronska, Joanna M.; Smialowska, Maria; Branski, Piotr; Gasparini, Fabrizio; Kłodzinska, Aleksandra; Szewczyk, Bernadeta; Palucha, Agnieszka; Chojnacka-Wojcik, Ewa; Pilc, Andrzej
 CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Pol.
 SOURCE: Neuropsychopharmacology (2004), 29(3), 514-521
 CODEN: NEROEW; ISSN: 0893-133X
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Several lines of evidence indicate that inhibition of the metabotropic glutamate (mGlu) receptor 5 produces anxiolytic-like effects in rodents. Peptide neurotransmitter neuropeptide Y (NPY) produces an anxiolytic effect in rats after intraventricular or intra-amgydalar administration. Many classes of anxiolytic drugs exert their effect through the GABA-benzodiazepine (BZD) receptor complex. Therefore, in the present study we have investigated whether the anxiolytic action of MPEP (2-methyl-6-(phenylethynyl)pyridine), an mGlu5 receptor antagonist, is mediated by a mechanism involving either the GABA-BZD receptor complex or NPY receptor. In the behavioral studies, the anxiolytic activity of MPEP (10 mg/kg, i.p.) was examined using plus-maze test. The BZD antagonist flumazenil (10 mg/kg, i.p.) was given to one group of rats and Y1 receptor antagonist BIBO 3304 ((R)-N-[4-(aminocarbonylaminomethyl) phenyl] methyl]-N2-(diphenylacetyl)-argininamide trifluoroacetate) 3304) (200 pmol/site, intra-amgydala) to the other. It was found that anxiolytic effects of MPEP were not changed by flumazenil, but were abolished by BIBO 3304. Immunohistochem. studies showed a high d. of mGlu5 receptor immunoreactivity (IR) in the amygdala. The effect of MPEP on NPY expression in the amygdala was studied using immunohistochem. (IH) and RIA. Both methods showed a diminution of NPY IR expression, to about 43% (IH) or 81% (RIA) of the control level after multiple administrations, but we observed an increase up to 148% of the control after single MPEP

administration. These effects may suggest a release of NPY from nerve terminals after MPEP administration. Our results indicate that the anxiolytic action of MPEP is conveyed through NPY neurons with the involvement of Y1 receptors in the amygdala and that BZD receptors do not significantly contribute to these effects.

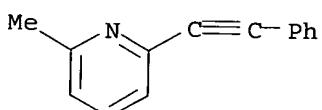
IT 96206-92-7, MPEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mGlu5 receptor antagonist MPEP involves NPY but not GABAA signaling where MPEP effect unchanged by flumazenil but abolished by BIBO 3304 indicate anxiolytic action of MPEP was via NPY neuron with Y1 receptor involvement in rat amygdala)

RN 96206-92-7 HCAPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:692210 HCAPLUS

DOCUMENT NUMBER: 140:139231

TITLE: A family of highly selective allosteric modulators of the metabotropic glutamate receptor subtype 5

AUTHOR(S): O'Brien, Julie A.; Lemaire, Wei; Chen, Tsing-Bau; Chang, Raymond S. L.; Jacobson, Marlene A.; Ha, Sookhee N.; Lindsley, Craig W.; Schaffhauser, Herve J.; Sur, Cyrille; Pettibone, Douglas J.; Conn, P. Jeffrey; Williams, David L., Jr.

CORPORATE SOURCE: Neuroscience-WP, Merck Research Laboratories, West Point, PA, USA

SOURCE: Molecular Pharmacology (2003), 64(3), 731-740

CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

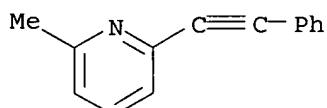
OTHER SOURCE(S): CASREACT 140:139231

AB We have identified a family of highly selective allosteric modulators of the group I metabotropic glutamate receptor subtype 5 (mGluR5). This family of closely related analogs exerts a spectrum of effects, ranging from pos. to neg. allosteric modulation, and includes compds. that do not themselves modulate mGluR5 agonist activity but rather prevent other family members from exerting their modulatory effects.

3,3'-Difluorobenzaldazine (DFB) has no agonist activity, but it acts as a selective pos. allosteric modulator of human and rat mGluR5. DFB potentiates threshold responses to glutamate, quisqualate, and 3,5-dihydroxyphenylglycine in fluorometric Ca²⁺ assays 3- to 6-fold, with EC50 values in the 2 to 5 μM range, and at 10 to 100 μM, it shifts mGluR5 agonist concentration-response curves approx. 2-fold to the left. The analog 3,3'-dimethoxybenzaldazine (DMeOB) acts as a neg. modulator of mGluR5 agonist activity, with an IC50 of 3 μM in fluorometric Ca²⁺ assays, whereas the analog 3,3'-dichlorobenzaldazine (DCB) does not exert any apparent modulatory effect on mGluR5 activity. However, DCB seems to

act as an allosteric ligand with neutral cooperativity, preventing the pos. allosteric modulation of mGluRs by DFB as well as the neg. modulatory effect of DMeOB. None of these analogs affects binding of [³H]quisqualate to the orthosteric (glutamate) site, but they do inhibit [³H]3-methoxy-5-(2-pyridinylethynyl)pyridine binding to the site for 2-methyl-6-(phenylethynyl)pyridine, a previously identified neg. allosteric modulator. With the use of these compds., we provide evidence that allosteric sites on GPCRs can respond to closely related ligands with a range of pharmacol. activities from pos. to neg. modulation as well as to neutral competition of this modulation.

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (effect of benzaldazine analog modulators on binding to the mGluR5 site for 2-methyl-6-(phenylethynyl)pyridine; preparation of a family of highly selective allosteric modulators of metabotropic glutamate receptor subtype 5)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 20 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:595237 HCPLUS
 DOCUMENT NUMBER: 140:70824
 TITLE: Neuroprotective action of MPEP, a selective mGluR5 antagonist, in methamphetamine-induced dopaminergic neurotoxicity is associated with a decrease in dopamine outflow and inhibition of hyperthermia in rats
 AUTHOR(S): Golembiowska, K.; Konieczny, J.; Wolfarth, S.; Ossowska, K.
 CORPORATE SOURCE: Institute of Pharmacology, Department of Pharmacology, Polish Academy of Sciences, Krakow, 31-343, Pol.
 SOURCE: Neuropharmacology (2003), 45(4), 484-492
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier Science B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The aim of this study was to examine the role of metabotropic glutamate receptor 5 (mGluR5) in the toxic action of methamphetamine on dopaminergic neurons in rats. Methamphetamine (10 mg/kg s.c.), administered five times, reduced the levels of dopamine and its metabolites in striatal tissue when measured 72 h after the last injection. A selective antagonist of mGluR5, 2-methyl-6-(phenylethynyl)pyridine (MPEP; 5 mg/kg i.p.), when administered five times immediately before each methamphetamine injection reversed the above-mentioned methamphetamine effects. A single MPEP (5 mg/kg i.p.) injection reduced the basal extracellular dopamine level in the striatum, as well as dopamine release stimulated either by methamphetamine (10 mg/kg s.c.) or by intrastriatally administered veratridine (100 μM). Moreover, it transiently diminished the methamphetamine (10 mg/kg s.c.)-induced hyperthermia and reduced basal body temperature MPEP administered into the striatum at high concns. (500

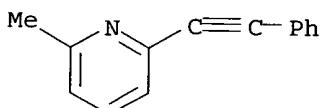
μM) increased extracellular dopamine levels, while lower concns. ($50-100 \mu\text{M}$) were devoid of any effect. The results of this study suggest that the blockade of mGluR5 by MPEP may protect dopaminergic neurons against methamphetamine-induced toxicity. Neuroprotection rendered by MPEP may be associated with the reduction of the methamphetamine-induced dopamine efflux in the striatum due to the blockade of extrastratal mGluR5, and with a decrease in hyperthermia.

IT 96206-92-7, MPEP

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective action of MPEP, selective mGluR5 antagonist, in methamphetamine-induced dopaminergic neurotoxicity is associated with decrease in dopamine, DOPAC, and HVA, and inhibition of hyperthermia)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 21 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:392445 HCPLUS

DOCUMENT NUMBER: 139:224807

TITLE: In vitro characterization of [^3H]MethoxyPyEP, an mGluR5 selective radioligand

AUTHOR(S): Patel, Shil; Krause, Stephen M.; Hamill, Terence; Chaudhary, Ashok; Burns, Donald H.; Gibson, Raymond A.

CORPORATE SOURCE: Department of Pharmacology and Imaging, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: Life Sciences (2003), 73(3), 371-379
CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have characterized the in vitro properties of 3-[^3H]methoxy-5-(pyridin-2-yethynyl)pyridine ([^3H]MethoxyPyEP), an analog of the mGluR5 receptor subtype antagonist MPEP [2-methyl-6-(phenylethynyl)-pyridine], in rat tissue preps. using tissue homogenates and autoradiog. Binding of [^3H]MethoxyPyEP to rat cortex, hippocampus, thalamus and cerebellum membrane preps. revealed saturable, high affinity binding ($3.4 \pm 0.4 \text{ nM}$, $n = 4$ in rat cortex) to a single population of receptors in all regions studied except for cerebellum. Binding was found to be relatively insensitive to pH and insensitive to DTT. High concns. of NEM both reduce receptor concentration and binding affinity for the radioligand. In time-course

studies at room temperature kon and koff were determined as $2.9 \pm 107 \text{ M}^{-1} \text{ min}^{-1}$ and 0.11 min^{-1} resp. The rank order of affinities, as assessed by equilibrium competition studies, of a variety of ligands suggested binding of the radioligand selectively to mGluR5 (MPEP > trans-azetidine-2,4-dicarboxylic acid .simeq. (S)-4-carboxyphenylglycine .simeq. (+)MK801 .simeq. CP-101,606 .simeq. clozapine .simeq. atropine .simeq. ketanserin .simeq. yohimbine .simeq. benoxathian). Autoradiog. studies with [^3H]MethoxyPyEP showed that binding was regioselective, with high d. of binding in caudate and hippocampus, intermediate binding in thalamus and very low d. in the

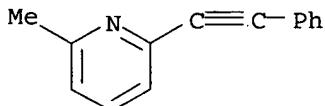
cerebellum. These data show that [³H]MethoxyPyEP is a high affinity radioligand useful for the *in vitro* study of mGluR5 receptor distribution and pharmacol. properties in brain.

IT 96206-92-7, MPEP

RL: PAC (Pharmacological activity); BIOL (Biological study)
(analog; *in vitro* characterization of [³H]MethoxyPyEP, an mGluR5 selective radioligand, tissue localization and pharmacol. competition with other ligands)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 22 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:368413 HCPLUS

DOCUMENT NUMBER: 139:358526

TITLE: The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice

AUTHOR(S): Paterson, Neil E.; Semenova, Svetlana; Gasparini, Fabrizio; Markou, Athina

CORPORATE SOURCE: CVN-7, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Psychopharmacology (Berlin, Germany) (2003), 167(3), 257-264

CODEN: PSCHDL; ISSN: 0033-3158

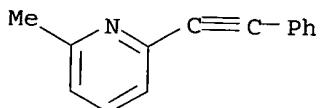
PUBLISHER: • Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

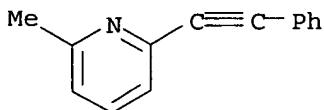
AB Rationale. Nicotine increases glutamate release in the ventral tegmental area and the nucleus accumbens, and thus enhances dopamine neurotransmission in the mesolimbic system that has been implicated in mediating the rewarding effects of drugs. Metabotropic glutamate receptors 5 (mGluR5) are found in the nucleus accumbens and may play a role in modulating the post-synaptic response to both glutamate and dopamine. Objectives. The present study investigated the effects of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) on i.v. nicotine self-administration in Wistar rats and DBA/2J mice. Methods. Rats were allowed to self-administer nicotine (0.01, 0.03 mg/kg per infusion) or respond for food on one of two fixed-ratio 5 schedules of reinforcement. Drug-naive mice were acutely exposed, in pairs, to nicotine (0, 0.016, 0.048, 0.16, 0.48 µg per infusion) self-administration under a fixed ratio 1 schedule of reinforcement, with one subject controlling the delivery of nicotine to both subjects in each pair. Results. MPEP (1-9 mg/kg) dose-dependently reduced nicotine self-administration with no effect on food-maintained responding in the rats. Self-administration of nicotine was obtained only at the 0.048 µg per infusion dose by the mice, and administration of MPEP (5-20 mg/kg) decreased nicotine self-administration response rates in the mice. Conclusions. These results indicate that blockade of mGluR5 decreased nicotine self-administration in both rats and mice, and are consistent with findings showing a role of mGluR5 in cocaine self-administration. It is postulated that mGluR5 plays an essential role in mediating the

IT reinforcing effects of nicotine, possibly but not exclusively, via modulation of mesolimbic dopaminergic neurotransmission.
 96206-92-7, 2-Methyl-6-(phenylethynyl) pyridine
 RL: PAC (Pharmacological activity); BIOL (Biological study)
 (mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:327228 HCAPLUS
 DOCUMENT NUMBER: 139:207605
 TITLE: The mGluR5 selective antagonist 6-methyl-2-(phenylethynyl)-pyridine reduces the spinal neuron pain-related activity in mononeuropathic rats
 Sotgiu, Maria Luisa; Bellomi, Paola; Biella, Gabriele E. M.
 CORPORATE SOURCE: Istituto di Bioimmagini e Fisiologia Molecolare, CNR, Segrate (Mi), 20090, Italy
 SOURCE: Neuroscience Letters (2003), 342(1,2), 85-88
 CODEN: NELED5; ISSN: 0304-3940
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB In rats with chronic constriction of one sciatic nerve (CCI rats), showing behavioral signs of neuropathic pain, 6-methyl-2-(phenylethynyl)-pyridine (MPEP), a selective mGluR5 antagonist, was i.p. administered at 0.75, 1.0 and 1.5 mg/kg or spinally microejected and the effects on the lumbar wide dynamic range neurons activity were investigated. In CCI rats MPEP at 1.0 and 1.5 (but not at 0.75) mg/kg, or spinally microejected induced a significant reduction of the spontaneous (SA) and noxious evoked activity (NEA), and a significant decrease of the suppression of the afterdischarge duration. In sham rats SA was unaffected and NEA was significantly reduced by 1.0 and 1.5 mg/kg MPEP dosages. These findings indicate that the metabotropic GluR5 receptor plays a role in the spinal cord processes underlying neuropathic pain and represents a potential target for new therapeutic approaches.
 IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 selective antagonist MPEP reduces spinal neuron pain-related activity in mononeuropathic rats)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 24 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:90448 HCPLUS

DOCUMENT NUMBER: 139:30641

TITLE: The mGluR5 antagonist MPEP reduces the conditioned rewarding effects of cocaine but not other drugs of abuse

AUTHOR(S): McGeehan, Andrew J.; Olive, M. Foster

CORPORATE SOURCE: Ernest Gallo Clinic & Research Center, Department of Neurology, University of California at San Francisco, Emeryville, CA, 94608, USA

SOURCE: Synapse (New York, NY, United States) (2003), 47(3), 240-242

CODEN: SYNAET; ISSN: 0887-4476

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We examined the ability of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a selective antagonist of the type 5 metabotropic glutamate receptor (mGluR5), to reduce the rewarding effects of various drugs of abuse in the conditioned place preference (CPP) paradigm. Mice were treated with MPEP (1, 5, and 20 mg/kg i.p.) 10 min prior to cocaine (15 mg/kg i.p.), D-amphetamine (2 mg/kg i.p.), nicotine (0.5 mg/kg i.p.), morphine (5 mg/kg i.p.), or ethanol (2 g/kg i.p.) on 3 successive days of CPP conditioning trials. MPEP pretreatment dose-dependently reduced the development of CPP for cocaine only. When tested alone at the doses effective in reducing CPP, MPEP produced neither a place preference nor aversion. These data provide further support for a role of the mGluR5 receptor in the rewarding effects of cocaine.

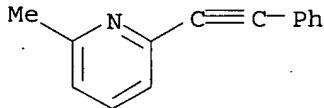
IT 96206-92-7, MPEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mGluR5 antagonist MPEP reduces conditioned rewarding effects of cocaine but not other drugs of abuse)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 25 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:53368 HCPLUS

DOCUMENT NUMBER: 139:63143

TITLE: Inhibitory effects of MPEP, an mGluR5 antagonist, and

AUTHOR(S): memantine, an N-methyl-D-aspartate receptor antagonist, on morphine antinociceptive tolerance in mice
 CORPORATE SOURCE: Kozela, Ewa; Pilc, Andrzej; Popik, Piotr Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31-343, Pol.
 SOURCE: Psychopharmacology (Berlin, Germany) (2003), 165(3), 245-251
 CODEN: PSCHDL; ISSN: 0033-3158
 PUBLISHER: Springer-Verlag
 DOCUMENT TYPE: Journal
 LANGUAGE: English

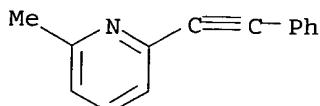
AB Rationale. Inhibition of N-methyl-D-aspartate (NMDA) receptors by memantine, an NMDA-receptor antagonist, and other antagonists of ionotropic receptors for glutamate inhibit the development of opiate antinociceptive tolerance. The role of metabotropic receptors for glutamate (mGluR) in opiate tolerance is less known. Objective. In the present study, we examined the effect of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), the mGluR type-I (subtype mGluR5) antagonist, as well as the effect of co-administration of low doses of memantine and MPEP on morphine antinociceptive tolerance in mice. Morphine antinociceptive activity was tested twice, before and after chronic morphine administration, in the tail-flick test using a cumulative dose-response protocol. Tolerance was induced by six consecutive days of b.i.d. administration of morphine (10 mg/kg, s.c.). Saline, memantine (7.5 mg/kg and 2.5 mg/kg, s.c.), MPEP (30 mg/kg and 10 mg/kg, i.p.) and the combination of both antagonists at low doses was given 30 min prior to each morphine injection during its chronic administration. A sep. experiment assessed the effects of memantine, MPEP and their combination on acute morphine antinociception using a tail-flick test. MPEP (30 mg/kg but not 10 mg/kg) as well as memantine (7.5 mg/kg but not 2.5 mg/kg) attenuated the development of tolerance to morphine-induced antinociception. When given together, the low doses of MPEP (10 mg/kg) and memantine (2.5 mg/kg) also significantly attenuated opiate tolerance. None of the treatments with glutamate antagonists produced antinociceptive effects or significantly affected morphine-induced antinociception. The data suggest that both mGluR5 and NMDA receptors may be involved in the development of morphine antinociceptive tolerance.

IT 96206-92-7, MPEP

RL: PAC (Pharmacological activity); BIOL (Biological study)
 (inhibitory effects of MPEP, an mGluR5 antagonist, and
 memantine, an N-Me-D-aspartate receptor antagonist, on morphine
 antinociceptive tolerance in mice)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 26 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:50605 HCPLUS

DOCUMENT NUMBER: 139:255247

TITLE: Selective blockade of mGlu5 metabotropic glutamate

AUTHOR(S) : receptors is protective against acetaminophen hepatotoxicity in mice
 Storto, Marianna; Ngomba, Richard Teke; Battaglia, Giuseppe; Freitas, Isabel; Griffini, Patrizia; Richelmi, Plinio; Nicoletti, Ferdinando; Vairetti, Mariapia

CORPORATE SOURCE: Loc. Camerelle, I.N.M. Neuromed, Pozzilli, 86077, Italy

SOURCE: Journal of Hepatology (2003), 38(2), 179-187
 CODEN: JOHEEC; ISSN: 0168-8278

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mGlu5 metabotropic glutamate receptor antagonists protect rat hepatocytes against hypoxic death. Here, we have examined whether mGlu5 receptor antagonists are protective against liver damage induced by oxidative stress. Toxicity of isolated hepatocytes was induced by tert-butylhydroperoxide (t-BuOOH) after pretreatment with the mGlu5 receptor antagonists, MPEP, SIB-1757 and SIB-1893. The effect of these drugs was also examined in mice challenged with toxic doses of acetaminophen. Addition of tBuOOH (0.5 mM) to isolated hepatocytes induced cell death ($70\pm5\%$ at 3 h). Addition of MPEP or SIB-1893 to hepatocytes reduced both the production of reactive oxygen species (ROS) and cell toxicity induced by t-BuOOH (tBuOOH = $70\pm5\%$; tBuOOH+MPEP = $57\pm6\%$; tBuOOH+SIB-1893 = $40\pm4\%$). In mice, a single injection of acetaminophen (300 mg/kg, i.p.) induced centrilobular liver necrosis, which was detectable after 24 h. MPEP (20 mg/kg, i.p.) substantially reduced liver necrosis and the production of ROS, although it did not affect the conversion of acetaminophen into the toxic metabolite, N-acetylbenzoquinoneimine. MPEP, SIB-1893 and SIB-1757 (all at 20 mg/kg, i.p.) also reduced the increased expression and activity of liver iNOS induced by acetaminophen. We conclude that pharmacol. blockade of mGlu5 receptors might represent a novel target for the treatment of drug-induced liver damage.

IT 7370-21-0, SIB-1893 96206-92-7, MPEP

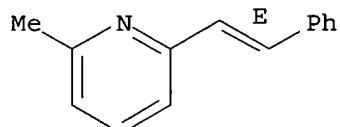
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(selective blockade of mGlu5 metabotropic glutamate receptors is protective against acetaminophen hepatotoxicity in mice)

RN 7370-21-0 HCPLUS

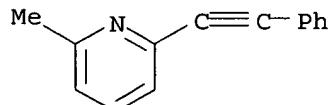
CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



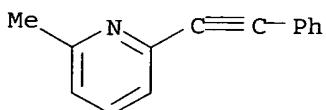
RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:27739 HCAPLUS
 DOCUMENT NUMBER: 139:30608
 TITLE: The mGluR5 antagonist MPEP, but not the mGluR2/3 agonist LY314582, augments PCP effects on prepulse inhibition and locomotor activity
 AUTHOR(S): Henry, S. A.; Lehmann-Masten, V.; Gasparini, F.; Geyer, M. A.; Markou, A.
 CORPORATE SOURCE: Departments of Neurosciences and Psychiatry, University of California, San Diego, La Jolla, CA, 92093, USA
 SOURCE: Neuropharmacology (2003), Volume Date 2002, 43(8), 1199-1209
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Phencyclidine (PCP), a non-competitive antagonist of ionotropic N-methyl-D-aspartate (NMDA) receptors, produces psychotomimetic effects, such as a disruption in prepulse inhibition (PPI) of the startle response. NMDA antagonists also induce locomotor hyperactivity in rodents. We hypothesized that, like NMDA receptors, metabotropic glutamate receptors (mGluRs) modulate PPI and locomotor activity either alone or, in the case of mGluR5, via interaction with NMDA receptors. Rats treated with the mGluR5 antagonist MPEP (2-methyl-6-phenylethynylpyridine) or the mGluR2/3 agonist LY314582, either alone or in combination with PCP, were tested in PPI and locomotor activity paradigms. Neither MPEP nor LY314582 altered PPI. MPEP, but not LY314582, potentiated the PPI-disruptive effects of PCP. MPEP alone did not alter locomotor or exploratory behavior, but augmented the complex, time-dependent locomotor-stimulating effects of PCP. LY314582 dose-dependently decreased locomotor activity and exploratory holepokes. LY314582 did not alter the PCP-induced increases in locomotor activity, but further decreased the number of holepokes. The effects of MPEP on the response to PCP may reflect the cooperation and co-localization of NMDA and mGlu5 receptors.
 IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); BIOL (Biological study)
 (the mGluR5 antagonist MPEP, but not the mGluR2/3 agonist LY314582, augments phencyclidine effects on prepulse inhibition and locomotor activity)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

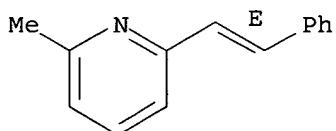
L36 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:777767 HCAPLUS
 DOCUMENT NUMBER: 137:273227

TITLE: Compositions and uses of mGluR5 antagonists
 INVENTOR(S): Bear, Mark F.; Huber, Kimberly M.
 PATENT ASSIGNEE(S): Brown University Research Foundation, USA
 SOURCE: PCT Int. Appl., 81 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
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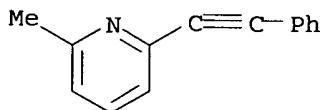
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078745	A2	20021010	WO 2002-US10211	20020402
WO 2002078745	A3	20021128		
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CA 2442478	AA	20021010	CA 2002-2442478	20020402
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US 2004067978	A1	20040408	US 2003-408771	20030404
US 6916821	B2	20050712		
US 2005171067	A1	20050804	US 2004-15328	20041217
PRIORITY APPLN. INFO.:			US 2001-280915P	P 20010402
			US 2002-114433	A2 20020402
			WO 2002-US10211	W 20020402
			US 2003-408771	A1 20030404

AB Compns. and uses of mGluR5 antagonists for the treatment and prevention of neurol. disorders, such as Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome, are disclosed.
 IT 7370-21-0, SIB 1893 96206-92-7
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (compns. and uses of mGluR5 antagonists)
 RN 7370-21-0 HCPLUS
 CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

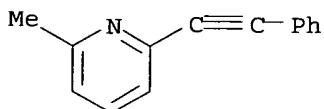
Double bond geometry as shown.



RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



L36 ANSWER 29 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:765433 HCPLUS
 DOCUMENT NUMBER: 138:314394
 TITLE: Antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in the olfactory bulbectomized rats
 AUTHOR(S): Wieronska, J. M.; Szewczyk, B.; Branski, P.; Palucha, A.; Pilc, A.
 CORPORATE SOURCE: Polish Academy of Sciences, Institute of Pharmacology, Krakow, Pol.
 SOURCE: Amino Acids (2002), 23(1-3), 213-216
 CODEN: AACIE6; ISSN: 0939-4451
 PUBLISHER: Springer-Verlag Wien
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Using the olfactory bulbectomy model of depression, we examined the antidepressant-like activity of 2-methyl-6-(phenylethynyl)-pyridine (MPEP) in rats. Bulbectomized rats required a significantly greater number of trials to acquire the response similar to sham-operated controls in the passive avoidance model. Both the prolonged (but not acute) treatment with MPEP and with antidepressant drug-desipramine restored the learning deficit. The results indicate that the prolonged blockade of mGlu5 receptors exerts antidepressant-like effects in rats.
 IT 96206-92-7, 2-Methyl-6-(phenylethynyl) pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in olfactory bulbectomized rats)
 RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

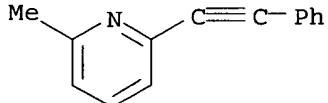
L36 ANSWER 30 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:512133 HCPLUS
 DOCUMENT NUMBER: 138:180494
 TITLE: Anxiolytic-like activity of the mGluR5 antagonist MPEP. A comparison with diazepam and buspirone
 AUTHOR(S): Brodkin, Jesse; Busse, Chris; Sukoff, Stacey J.; Varney, Mark A.
 CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, 92121, USA
 SOURCE: Pharmacology, Biochemistry and Behavior (2002), 73(2), 359-366

CODEN: PBBHAU; ISSN: 0091-3057

PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The selective and systemically active antagonist for the metabotropic glutamate receptor subtype 5 (mGluR5), 2-methyl-6-(phenylethynyl)pyridine (MPEP) was shown to display anxiolytic-like activity in a number of unconditioned assays of stress and anxiety (elevated plus maze, shock probe burying, marble burying, social interaction, and stress-induced hyperthermia) in rodents. In this report, we extend these observations found using unconditioned models of anxiety to include three models of conditioned anxiety, comparing the activity of MPEP to the clin. used anxiolytics, diazepam, and buspirone. MPEP and diazepam, but not buspirone, showed anxiolytic-like activity in the fear-potentiated startle (FPS) model. In a conditioned ultrasonic vocalization (USV) procedure, MPEP, diazepam, and buspirone reduced vocalizations to a similar degree. In the modified Geller-Seifter procedure, MPEP, diazepam, and buspirone displayed statistically significant anxiolytic-like activity, increasing the number of punished responses. Thus, these findings confirm and extend previous reports that MPEP exhibits anxiolytic-like activity in rats, and suggests that development of mGluR5 antagonists may provide a novel approach to treating anxiety disorders.

IT 96206-92-7, MPEP
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (anxiolytic-like activity of mGluR5 antagonist MPEP)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:243372 HCAPLUS
 DOCUMENT NUMBER: 137:119502
 TITLE: Selective blockade of mGlu5 metabotropic glutamate receptors is protective against methamphetamine neurotoxicity
 AUTHOR(S): Battaglia, Giuseppe; Fornai, Francesco; Busceti, Carla L.; Aloisi, Gabriella; Cerrito, Franca; De Blasi, Antonio; Melchiorri, Daniela; Nicoletti, Ferdinando
 CORPORATE SOURCE: Instituto Neuromed Mediterraneo, Pozzilli (Isernia), 86077, Italy
 SOURCE: Journal of Neuroscience (2002), 22(6), 2135-2141
 CODEN: JNRSDS; ISSN: 0270-6474
 PUBLISHER: Society for Neuroscience
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Methamphetamine (MA), a widely used drug of abuse, produces oxidative damage of nigrostriatal dopaminergic terminals. We examined the effect of subtype-selective ligands of metabotropic glutamate (mGlu) receptors on MA neurotoxicity in mice. MA (5 mg/kg, i.p.; injected three times, every 2 h) induced, 5 d later, a substantial degeneration of

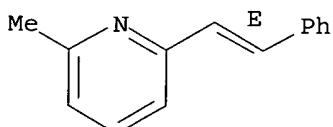
striatal dopaminergic terminals associated with reactive gliosis. MA toxicity was primarily attenuated by the coinjection of the noncompetitive mGlu5 receptor antagonists 2-methyl-6-(phenylethynyl)pyridine and (E)-2-methyl-6-styrylpyridine both at 10 mg/kg, i.p.. In contrast, the mGlu1 receptor antagonist 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate Et ester (10 mg/kg, i.p.), and the mGlu2/3 receptor agonist (-)-2-oxa-4-aminocyclo[3.1.0]hexane-4,6-dicarboxylic acid (1 mg/kg, i.p.), failed to affect MA toxicity. MGLu5 receptor antagonists reduced the production of reactive oxygen species but did not reduce the acute stimulation of dopamine release induced by MA both in striatal synaptosomes and in the striatum of freely moving mice. We conclude that endogenous activation of mGlu5 receptors enables the development of MA neurotoxicity and that mGlu5 receptor antagonists are neuroprotective without interfering with the primary mechanism of action of MA.

IT 7370-21-0, SIB-1893 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (selective blockade of mGlu5 receptors is protective against methamphetamine neurotoxicity)

RN 7370-21-0 HCAPLUS

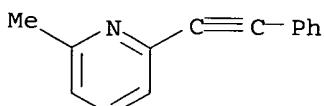
CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 96206-92-7 HCAPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:898996 HCAPLUS

DOCUMENT NUMBER: 136:303937

TITLE: Selective mGluR5 receptor antagonist or agonist provides neuroprotection in a rat model of focal cerebral ischemia

AUTHOR(S): Bao, W. L.; Williams, A. J.; Faden, A. I.; Tortella, F. C.

CORPORATE SOURCE: Department of Neuroscience, Georgetown University Medical Center, Washington, DC, 20007, USA

SOURCE: Brain Research (2001), 922(2), 173-179
 CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

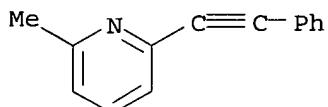
AB Activation of group I metabotropic glutamate receptors (mGluR) has been implicated in the pathophysiol. of acute central nervous system injury. However, the relative roles of the two group I subtypes, mGluR1 or mGluR5, in such injury has not been well examined. This study compared the effects of treatment with the newly developed, selective mGluR5 antagonist 2-methyl-6-phenylethynylpyridine (MPEP) and the selective mGluR5 agonist (R,S)-2-chloro-5-hydroxyphenylglycine (CHPG) in a rat intraluminal filament model of temporary middle cerebral artery occlusion. Rats were administered MPEP or CHPG intracerebroventricularly beginning 15 or 135 min after induction of 2-h ischemia. Infarct size was measured after either 22 or 70 h of reperfusion, and neurol. function was quantified after 2, 24, 48 and 72 h. Treatment with MPEP or CHPG after 15 min reduced 24-h infarct volume by 61 and 44%, resp. The neuroprotective effects were dose dependent. Delaying MPEP treatment until 135 min eliminated the neuroprotective effects. With early MPEP treatment (15 min) at optimal doses, infarct volume was reduced by 44% after 72 h, and this was correlated with significant neurol. recovery. These data suggest that both MPEP and CHPG are neuroprotective when administered after focal cerebral ischemia. Other studies showed that although MPEP does act as an mGluR5 antagonist and blocks agonist-induced phosphoinositide hydrolysis, it also serves as a noncompetitive NMDA antagonist; in contrast, CHPG-mediated neuroprotection may reflect antiapoptotic activity. Therefore, both types of compds. may prove to have therapeutic potential for the treatment of stroke.

IT 96206-92-7, MPEP

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 receptor antagonist MPEP or agonist CHPG
 neuroprotection in focal cerebral ischemia)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 33 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:735073 HCPLUS

DOCUMENT NUMBER: 136:80105

TITLE: Characterization of a metabotropic glutamate receptor type 5-green fluorescent protein chimera (mGluR5-GFP): pharmacology, surface expression, and differential effects of Homer-1a and Homer-1c

AUTHOR(S): Coutinho, Victoria; Kavanagh, Irene; Sugiyama, Hiroyuki; Tones, Michael A.; Henley, Jeremy M.

CORPORATE SOURCE: MRC Centre for Synaptic Plasticity, Department of Anatomy, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK

SOURCE: Molecular and Cellular Neuroscience (2001), 18(3), 296-306

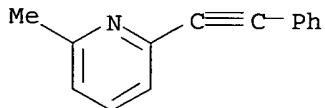
PUBLISHER: CODEN: MOCNED; ISSN: 1044-7431

Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

- AB Metabotropic glutamate receptor 5 (mGluR5) can modulate synaptic transmission by increasing intracellular Ca²⁺ and it plays a role in several forms of synaptic plasticity. The authors have constructed a fusion of human mGluR5 and green fluorescent protein (mGluR5-GFP). Expression of mGluR5-GFP in clonal cell lines yielded a functional fluorescent receptor with pharmacol. profiles similar to wild-type mGluR5. mGluR5-GFP coimmunopptd. with Homer-1c, indicating that addition of GFP to the C-terminal did not prevent Homer binding. Coexpression of wild-type mGluR5 or mGluR5-GFP with Homer 1c, but not Homer-1a, resulted in reduced receptor surface localization and the formation of intracellular clusters. Neither Homer-1a nor Homer-1c had any effect on mGluR1 or mGluR1-GFP distribution. mGluR5-GFP expressed alone or in combination with Homer-1a formed dimers in HEK cells. Coexpression with Homer-1c, however, prevented mGluR5-GFP dimerization. Neither Homer altered the agonist profiles of mGluR5 or mGluR5-GFP. These data indicate that the functional expression of mGluR5 is regulated by Homer-1c and demonstrate that mGluR5-GFP provides a useful tool to study the mol. pharmacol. and cell biol. of mGluRs in real-time. (c) 2001 Academic Press.
- IT 96206-92-7, MPEP
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (characterization of metabotropic glutamate receptor type 5-green fluorescent protein chimera (mGluR5-GFP) in relation to pharmacol., surface expression and differential effects of Homer-1a and Homer-1c in HEK-293 and CHO-K1 cells)
- RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

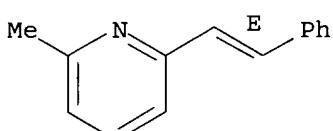
- L36 ANSWER 34 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:8414 HCPLUS
 DOCUMENT NUMBER: 134:202633
 TITLE: mGluR5 antagonists 2-methyl-6-(phenylethynyl)-pyridine and (E)-2-methyl-6-(2-phenylethenyl)-pyridine reduce traumatic neuronal injury in vitro and in vivo by antagonizing N-methyl-D-aspartate receptors
 AUTHOR(S): Movsesyan, Vilen A.; O'Leary, Deirdre M.; Fan, Lei; Bao, Weili; Mullins, Paul G. M.; Knoblach, Susan M.; Faden, Alan I.
 CORPORATE SOURCE: Georgetown Institute for Cognitive and Computational Sciences, Department of Neuroscience, Georgetown University Medical Center, Washington, DC, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 296(1), 41-47
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The effect of selective group I metabotropic glutamate receptor subtype 5 (mGluR5) antagonists 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and

(E)-2-methyl-6-(2-phenylethenyl)-pyridine (SIB-1893) on neuronal cell survival and post-traumatic recovery was examined using rat in vitro and in vivo trauma models. Treatment with MPEP and SIB-1893 showed significant neuro-protective effects in rat cortical neuronal cultures subjected to mech. injury. Application of the antagonists also attenuated glutamate- and N-methyl-D-aspartate (NMDA)-induced neuronal cell death in vitro. Intracerebroventricular administration of MPEP to rats markedly improved motor recovery and reduced deficits of spatial learning after lateral fluid percussion-induced traumatic brain injury. Lesion vols. as assessed by magnetic resonance imaging were also substantially reduced by MPEP treatment. Although we show that MPEP acts as a potent mGluR5 antagonist in our culture system, where it completely blocks agonist-induced phosphoinositide hydrolysis, electrophysiol. and pharmacol. studies indicate that MPEP and SIB-1893 also inhibit NMDA receptor activity at higher concns. that are neuroprotective. Taken together, these data suggest that MPEP and SIB-1893 may have therapeutic potential in brain injury, although the mechanisms of neuroprotective action for these drugs may reflect their ability to modulate NMDA receptor activity.

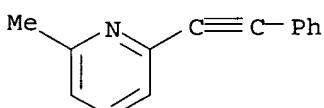
IT 7370-21-0, SIB-1893 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mGluR5 antagonists reduce traumatic neuronal injury by antagonizing NMDA receptors)

RN 7370-21-0 HCPLUS
 CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 96206-92-7 HCPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 35 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:898376 HCPLUS
 DOCUMENT NUMBER: 134:188129
 TITLE: Selective mGluR5 antagonists MPEP and SIB-1893 decrease NMDA or glutamate-mediated neuronal toxicity through actions that reflect NMDA receptor antagonism
 AUTHOR(S): O'Leary, Deirdre M.; Movsesyan, Vilen; Vicini, Stefano; Faden, Alan I.
 CORPORATE SOURCE: Department of Neuroscience, Georgetown University

SOURCE: Medical Center, Washington, DC, 20007, USA
 British Journal of Pharmacology (2000), 131(7),
 1429-1437

PUBLISHER: CODEN: BJPCBM; ISSN: 0007-1188
 Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English

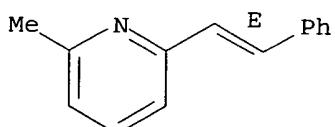
AB The metabotropic glutamate receptors (mGluRs) are a family of G-protein linked receptors that can be divided into three groups (group I, II and III). A number of studies have implicated group I mGluR activation in acute neuronal injury, but until recently it was not possible to pharmacol. differentiate the roles of the two individual subunits (mGluR1 and mGluR5) in this group. We investigated the role of mGluR5 in acute NMDA and glutamate mediated neurodegeneration in cultured rat cortical cells using the mGluR5 antagonists MPEP and SIB-1893, and found that they provide significant protection at concns. of 20 or 200 μ M. These compds. act as effective mGluR5 antagonists in our cell culture system, as indicated by the ability of SIB-1893 to prevent phosphoinositol hydrolysis induced by the specific mGluR5 agonist, (RS)-2-chloro-5-hydroxyphenylglycine (CHPG). However, they also significantly reduce NMDA evoked current recorded from whole cells voltage clamped at -60 mV, and significantly decrease the duration of opening of NMDA channels recorded in the outside out patch configuration. This suggests that although MPEP and SIB-1893 are effective mGluR5 antagonists, they also act as noncompetitive NMDA receptor antagonists. Therefore, the neuroprotective effects of these compds. are most likely mediated through their NMDA receptor antagonist action, and caution should be exercised when drawing conclusions about the roles of mGluR5 based on their use.

IT 7370-21-0, SIB-1893 96206-92-7, MPEP
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (selective mGluR5 antagonists MPEP and SIB-1893 decrease NMDA or glutamate-mediated neuronal toxicity through actions that reflect NMDA receptor antagonism)

RN 7370-21-0 HCPLUS

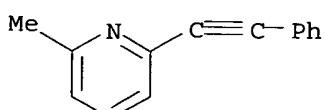
CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



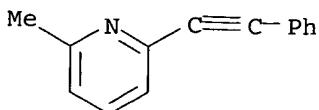
RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethyynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:806926 HCAPLUS
 DOCUMENT NUMBER: 134:51745
 TITLE: mGlu5 receptors and nociceptive function. II. mGlu5 receptors functionally expressed on peripheral sensory neurones mediate inflammatory hyperalgesia
 AUTHOR(S): Walker, K.; Reeve, A.; Bowes, M.; Winter, J.; Wotherspoon, G.; Davis, A.; Schmid, P.; Gasparini, F.; Kuhn, R.; Urban, L.
 CORPORATE SOURCE: Novartis Pharma AG Nervous System Research, Novartis Pharma AG, Basel, CH-4002, Switz.
 SOURCE: Neuropharmacology (2000), Volume Date 2001, 40(1), 10-19
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Previous studies have demonstrated that the metabotropic glutamate receptor subtype 5 (mGlu5 receptor) is expressed in the cell bodies of rat primary afferent neurons. The authors have further investigated the function and expression of mGlu5 receptors in primary afferent neurons, and their role in inflammatory nociception. Freund's complete adjuvant-induced inflammatory hyperalgesia of the rat hind paw was significantly reduced by intraplantar, but not by intracerebroventricular or intrathecal microinjection of the selective mGlu5 receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP). Pharmacol. comparison in vivo of the nociceptive effects of glutamate, and ionotropic and metabotropic glutamate (mGlu) receptor agonists applied to the rat hind paw, indicated that group I mGlu receptor agonists induce a dose-dependent decrease in paw withdrawal threshold (mech. hyperalgesia). Group I mGlu agonist-induced hyperalgesia was inhibited by co-microinjection of MPEP, but not by the mGlu1 receptor antagonist (S)-4-carboxy-phenylglycine (4-CPG). Carrageenan-induced inflammatory hyperalgesia was inhibited by pre-treatment of the inflamed hind paw with MPEP, but not following MPEP injection into the contralateral hind paw. Dorsal horn neurons receiving peripheral nociceptive and non-nociceptive afferent input were recorded in anesthetized rats following microinjection of CHPG into their peripheral receptive fields. CHPG significantly increased the frequency and duration of firing of dorsal horn wide dynamic range (WDR) neurons and this activity was prevented by co-administration of CHPG and MPEP into their receptive fields. Immunohistochem. expts. revealed the co-expression of mGlu5 receptor protein and β III tubulin in skin from naive rats, indicating the constitutive expression of mGlu5 receptors on peripheral neurons. Double-labeling of adult rat DRG cells with mGlu5 receptor and vanilloid receptor subtype 1 antisera also supports the expression of mGlu5 receptors on peripheral nociceptive afferents. These results suggest that mGlu5 receptors expressed on the peripheral terminals of sensory neurons are involved in nociceptive processes and contribute to the hyperalgesia associated with inflammation.
 IT 96206-92-7
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (pre-treatment of inflamed rat hind paw with mGlu5 receptor antagonist inhibits inflammatory hyperalgesia)
 RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 37 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:806925 HCPLUS

DOCUMENT NUMBER: 134:157470

TITLE: Metabotropic glutamate receptor subtype 5 (mGlu5) and nociceptive function. I. Selective blockade of mGlu5 receptors in models of acute, persistent and chronic pain

AUTHOR(S): Walker, K.; Bowes, M.; Panesar, M.; Davis, A.; Gentry, C.; Kesingland, A.; Gasparini, F.; Spooren, W.; Stoehr, N.; Pagano, A.; Flor, P. J.; Vranesic, I.; Lingenhoehl, K.; Johnson, E. C.; Varney, M.; Urban, L.; Kuhn, R.

CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, CH-4002, Switz.

SOURCE: Neuropharmacology (2000), Volume Date 2001, 40(1), 1-9
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The excitatory neurotransmitter, glutamate, is particularly important in the transmission of pain information in the nervous system through the activation of ionotropic and metabotropic glutamate receptors. A potent, subtype-selective antagonist of the metabotropic glutamate-5 (mGlu5) receptor, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), has now been discovered that has effective anti-hyperalgesic effects in models of inflammatory pain. MPEP did not affect rotarod locomotor performance, or normal responses to noxious mech. or thermal stimulation in naive rats. However, in models of inflammatory pain, systemic administration of MPEP produced effective reversal of mech. hyperalgesia without affecting inflammatory edema. In contrast to the non-steroidal anti-inflammatory drugs, indomethacin and diclofenac, the maximal anti-hyperalgesic effects of orally administered MPEP were observed without acute erosion of the gastric mucosa. In contrast to its effects in models of inflammatory pain, MPEP did not produce significant reversal of mech. hyperalgesia in a rat model of neuropathic pain.

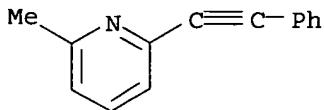
IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(metabotropic glutamate receptor subtype 5 (mGlu5) and nociceptive function. I. Selective blockade of mGlu5 receptors in models of acute, persistent and chronic pain)

RN 96206-92-7 HCPLUS

CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 38 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:736083 HCPLUS

DOCUMENT NUMBER: 134:95397

TITLE: Effects of the prototypical mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine on rotarod, locomotor activity and rotational responses in unilateral 6-OHDA-lesioned rats

AUTHOR(S): Spooren, W. P. J. M.; Gasparini, F.; Bergmann, R.; Kuhn, R.

CORPORATE SOURCE: Novartis Pharma AG, Nervous System Research, Basel, CH-4002, Switz.

SOURCE: European Journal of Pharmacology (2000), 406(3), 403-410

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

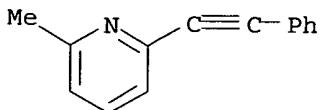
AB In the present study, we evaluated the effect of the prototypical metabotropic glutamate receptor 5 (mGlu5) antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) on motor behavior in rats using the accelerating rotarod, spontaneous locomotor activity and the 6-hydroxy-dopamine (6-OHDA) lesion model to assess its treatment potential for Parkinson's disease. The data indicate that MPEP at doses between 7.5 and 300 mg/kg, p.o. did not disrupt endurance performance on the accelerating rotarod (4-40 rpm in 300 s) which indicates that MPEP has a relatively high safety margin. However, while ineffective at doses of 3.75, 7.5 and 15 mg/kg (p.o.) MPEP inhibited spontaneous locomotor activity at doses of 30 and 100 mg/kg (p.o.). In the 6-OHDA rat rotation model, at doses of 7.5, 15 and 30 mg/kg (p.o.), MPEP induced a dose-dependent ipsilateral rotational response that reached statistical significance at the highest dose tested. This effect was relatively small but consistent. In combination with direct or indirect dopamine agonists, i.e. apomorphine (0.25 mg/kg, s.c.) and d-amphetamine (2.5 mg/kg, i.p.), MPEP (7.5, 15 or 30 mg/kg, p.o.) was found to significantly inhibit these dopamine receptor-mediated rotational responses. MPEP injected at a dose of 30 mg/kg also inhibited the rotational response induced by l-DOPA (25 mg/kg, i.p.). (+)MK-801 was used in these rotation expts. as the reference compound. In view of these findings, it could be concluded that MPEP and potentially other mGlu5 receptor antagonists are probably not appropriate drug candidates for the symptomatic treatment of Parkinson's disease.

IT 96206-92-7

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of the prototypical mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine on rotarod, locomotor activity and rotational responses in unilateral 6-OHDA-lesioned rats)

RN 96206-92-7 HCPLUS

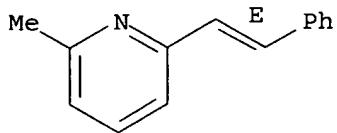
CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



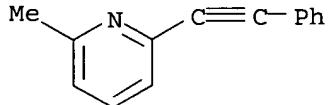
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 39 OF 39 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:395973 HCPLUS
 DOCUMENT NUMBER: 133:217631
 TITLE: Anticonvulsant activity of two metabotropic glutamate Group I antagonists selective for the mGlu5 receptor: 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and (E)-6-methyl-2-styryl-pyridine (SIB 1893)
 AUTHOR(S): Chapman, A. G.; Nanan, K.; Williams, M.; Meldrum, B. S.
 CORPORATE SOURCE: Department of Clinical Neurosciences, Institute of Psychiatry, London, SE5 8AF, UK
 SOURCE: Neuropharmacology (2000), 39(9), 1567-1574
 CODEN: NEPHBW; ISSN: 0028-3908
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The selective mGlu5 antagonists, MPEP, 2-methyl-6-phenylethynyl-pyridine, and SIB1893, (E)-6-methyl-2-styryl-pyridine, have been evaluated as antiepileptic drugs in DBA/2 mice and lethargic mice. Clonic seizures induced by the selective mGlu5 agonist, (R,S)-2-chloro-5-hydroxyphenylglycine (CHPG), 3 µmol intracerebroventricularly (i.c.v.), are potently suppressed by both compds. (MPEP, ED50=0.42 [0.28-0.62] mg/kg i.p. (i.p.); SIB 1893 ED50=0.19 [0.11-0.33] mg/kg i.p.). Clonic seizures induced by the mGlu1,5 agonist, 3,5-dihydroxyphenylglycine (DHPG), 1.5 µmol i.c.v., are less potently suppressed by both compds. (MPEP, ED50=22 [13-38] mg/kg i.p., 110 [67-180] nmol i.c.v.; SIB1893, ED50=31 [18-54] mg/kg i.p., 95 [82-110] nmol i.c.v.). Sound-induced seizures in DBA/2 mice are suppressed at 15 min by MPEP and SIB 1893 (MPEP ED50 clonic seizures=18 [10-32] mg/kg i.p., 93 [69-125] nmol i.c.v.; tonic seizures=6.1 [4.5-8.3] mg/kg i.p., 46 [26-80] nmol i.c.v.; SIB 1893 ED50 clonic seizures=27 [17-44] mg/kg i.p., 825 [615-1108] nmol i.c.v., tonic seizures=5.4 [3.4-8.6] mg/kg i.p., 194 [113-332] nmol i.c.v.). The ED50 for MPEP for impaired rotarod performance is 128 [83-193] mg/kg i.p., at 15 min, i.e. a therapeutic index for sound-induced seizures of 5-20. In lethargic mice (lh/lh), a genetic absence model, MPEP, 50 mg/kg i.p., caused a marked reduction in the incidence of spontaneous spike-and-wave discharges. These selective antagonists of mGlu5 block seizures due to activation of mGlu5 at very low systemic doses. At rather higher doses they block convulsive and non-convulsive primary generalized seizures.
 IT 7370-21-0, SIB 1893 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (anticonvulsant activity of two metabotropic glutamate Group I antagonists MPEP and SIB 1893 selective for mGlu5 receptor)
 RN 7370-21-0 HCPLUS
 CN Pyridine, 2-methyl-6-[(1E)-2-phenylethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

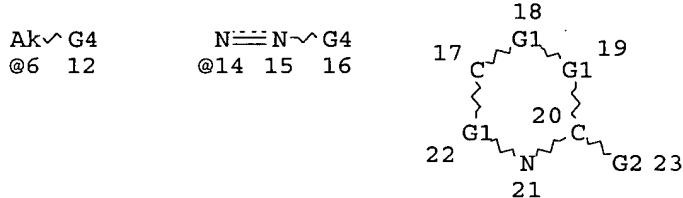


RN 96206-92-7 HCAPLUS
 CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4      46 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR MTEP
L5      34433 SEA FILE=HCAPLUS ABB=ON PLU=ON ("OVERACTIVE BLADDER"/CV OR
          "BLADDER, DISEASE (L) OVERACTIVE BLADDER"/CV) OR BLADDER
L7      148785 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR URINARY? OR ?CYSTITIS?
          OR URINE (2A) LEAK? OR ENURESIS OR BED(W) WETTING
L8      1 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND L7
L9      45 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 NOT L8
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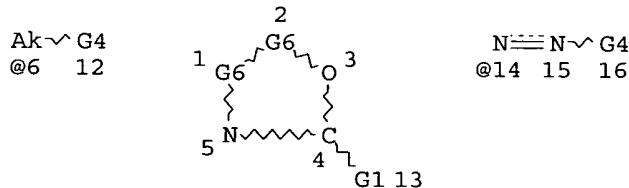


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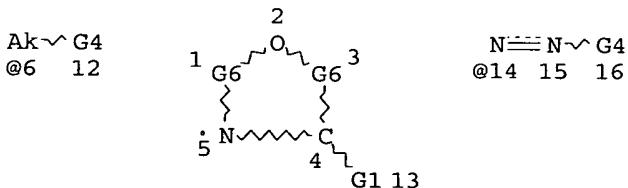
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OR TOLTERODINE OR DARIFENACIN OR TEMIVERINE
 L24 0 SEA FILE=REGISTRY ABB=ON PLU=ON ADRENERGIC(L)ANTAGONIS(L) (ALP
HA OR "A") (L)1
 L25 39 SEA FILE=REGISTRY ABB=ON PLU=ON L24 OR PRAZOSIN OR DOXAZOSIN
OR TERAZOSIN OR ALFUZOSIN OR TAMSULOSIN
 L26 1150 SEA FILE=HCAPLUS ABB=ON PLU=ON L22 OR MGLU5 OR MGLUR5 OR
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 L27 2191 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 OR ?ANTIMUSCARIN? OR
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 L33 78 SEA FILE=HCAPLUS ABB=ON PLU=ON L18(L)L26
 L34 51 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND (?DRUG? OR ?MEDICIN?
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 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
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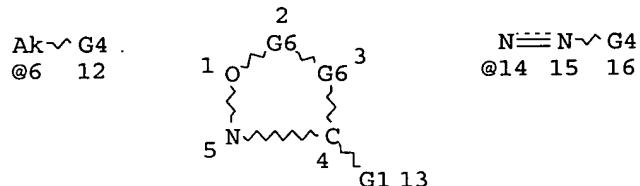
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NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE

L39 STR



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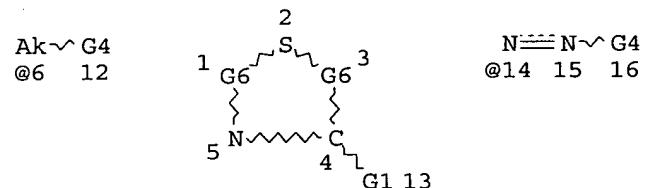
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NUMBER OF NODES IS 11

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L41 STR



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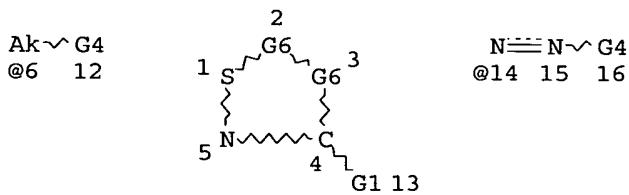
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NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE

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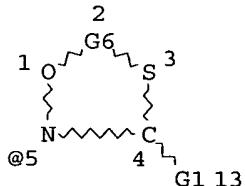
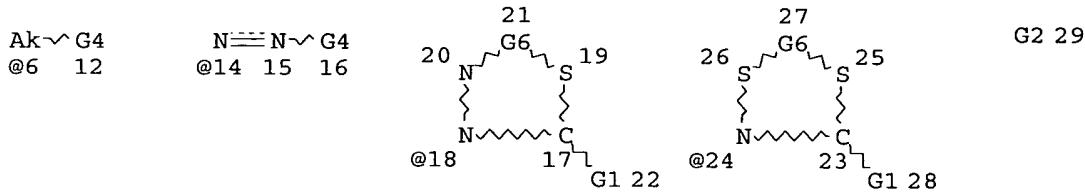


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VAR G6=C/O/N/S
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GRAPH ATTRIBUTES:

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RSPEC 4
NUMBER OF NODES IS 11
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STEREO ATTRIBUTES: NONE
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DEFAULT MLEVEL IS ATOM
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NUMBER OF NODES IS 24
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STEREO ATTRIBUTES: NONE
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L47 226119 SEA FILE=REGISTRY ABB=ON PLU=ON L46 NOT (L18 OR L1)
L48 42397 SEA FILE=HCAPLUS ABB=ON PLU=ON L47
L50 30 SEA FILE=HCAPLUS ABB=ON PLU=ON L48 AND L26
L53 222 SEA FILE=HCAPLUS ABB=ON PLU=ON L48 AND (L27 OR L28)
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L61 ANSWER 1 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:666025 HCAPLUS
 TITLE: Method for inducing crystalline state transition in pharmaceuticals
 INVENTOR(S): Nakamichi, Kouichi; Izumi, Shougo; Oka, Masaaki
 PATENT ASSIGNEE(S): Nippon Shinyaku Company, Ltd., Japan
 SOURCE: U.S., 18 pp., Cont.-in-part of U. S. 5,456,923.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5811547	A	19980922	US 1995-416815	19950609 <--
CA 2147279	AA	19940428	CA 1993-2147279	19931013 <--
WO 9408561	A1	19940428	WO 1993-JP1469	19931013 <--
W: AU, BR, CA, FI, HU, JP, KR, NO, NZ, RU, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9351607	A1	19940509	AU 1993-51607	19931013 <--
EP 665009	A1	19950802	EP 1993-922625	19931013 <--
EP 665009	B1	20000216		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 189770	E	20000315	AT 1993-922625	19931013 <--
ES 2145063	T3	20000701	ES 1993-922625	19931013 <--
US 5456923	A	19951010	US 1993-129133	19931115 <--
PRIORITY APPLN. INFO.:			JP 1992-303085	A 19921014
			WO 1993-JP1469	W 19931013
			US 1993-129133	A2 19931115
			JP 1991-112554	A 19910416
			WO 1992-JP470	W 19920414

AB This invention has for its object to provide a method of inducing a transition in crystalline state of a crystallizable pharmaceutical with great ease and improved efficiency and uniformity on a high production scale. An extruder is used for inducing a transition from one crystalline state (Δ) to another crystalline state in a crystallizable pharmaceutical. An extruded indomethacin (form α) was converted to an amorphous form.

IT INDEXING IN PROGRESS

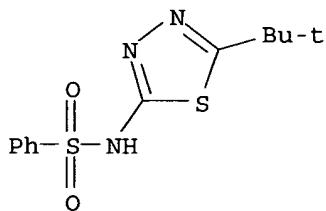
IT 1492-02-0, Glybzazole 1508-65-2, Oxybutynin hydrochloride 19237-84-4, Prazosin hydrochloride 21256-18-8, Oxaprozin 63074-08-8, Terazosin hydrochloride 77883-43-3, Doxazosin mesylate
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(method for inducing crystalline state transition in pharmaceuticals)

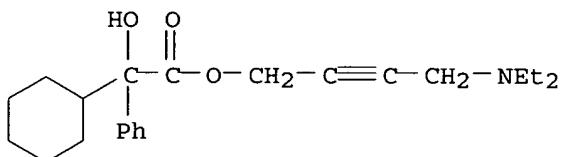
RN 1492-02-0 HCAPLUS

CN Benzenesulfonamide, N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]- (9CI)

(CA INDEX NAME)



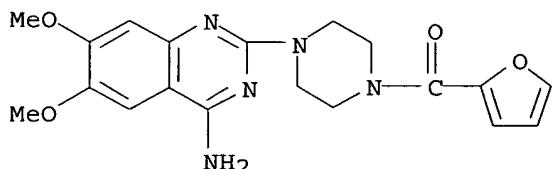
RN 1508-65-2 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 19237-84-4 HCPLUS

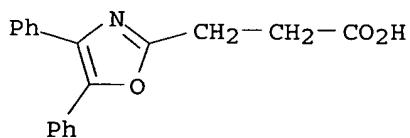
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

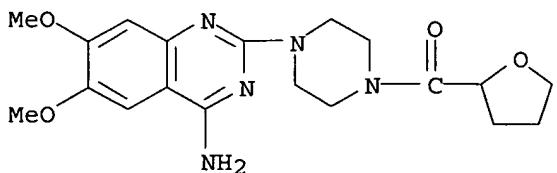
RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63074-08-8 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

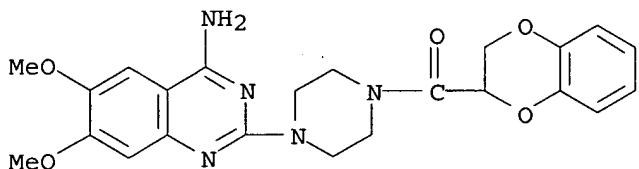
RN 77883-43-3 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8

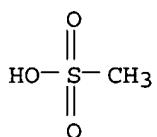
CMF C23 H25 N5 O5



CM 2

CRN 75-75-2

CMF C H4 O3 S



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 2 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1311702 HCPLUS

DOCUMENT NUMBER: 144:57525

TITLE: Coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents

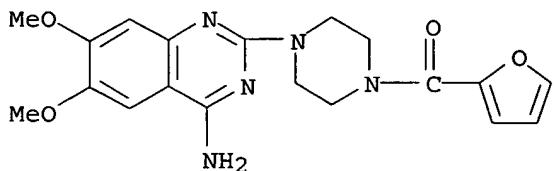
INVENTOR(S): Wilson, Michelle; Desai, Kishorkumar J.; Pauletti, Giovanni M.; Antoon, Mitchell K.; Clendening, Chris E.

PATENT ASSIGNEE(S) : USA
 SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S.
 Ser. No. 126,863
 CODEN: USXXCO

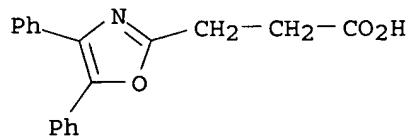
DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 11
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005276836	A1	20051215	US 2005-180076	20050712
US 6197327	B1	20010306	US 1998-79897	19980515 <--
US 6086909	A	20000711	US 1999-249963	19990212 <--
US 6572874	B1	20030603	US 2000-626025	20000727 <--
NZ 508130	A	20020301	NZ 2000-508130	20001113 <--
AU 765269	B2	20030911	AU 2001-54192	20010703 <--
US 2003049302	A1	20030313	US 2002-226667	20020821 <--
US 6982091	B2	20060103		
US 2004005345	A1	20040108	US 2003-349029	20030122
US 6905701	B2	20050614		
US 2004043071	A1	20040304	US 2003-600849	20030620
US 2005249774	A1	20051110	US 2005-126863	20050510
US 2006002966	A1	20060105	US 2005-208209	20050818
PRIORITY APPLN. INFO.:				
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			US 1998-79897	A2 19980515
			US 1999-249963	A2 19990212
			US 2000-626025	A2 20000727
			US 2002-226667	A2 20020821
			US 2003-349029	A2 20030122
			US 2003-600849	A2 20030620
			US 2004-587454P	P 20040712
			US 2005-126863	A2 20050510
			AU 1998-76976	A3 19980610
			NZ 1998-502120	A1 19980610
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			US 2001-315877P	P 20010829
			US 2002-390748P	P 20020621

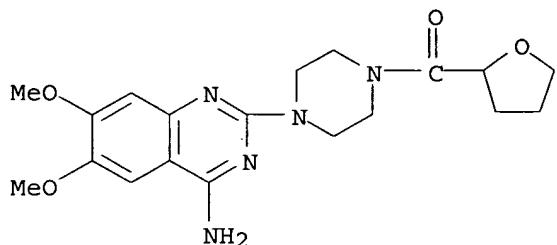
- AB Disclosed is a vaginal device for delivering therapeutical and/or health-promoting agents. The vaginal device partly or completely coated by, covered by or combined with a coating or covering comprising a film, foam, strip, cap, cup or particles. The coating of the device comprises a mucoadhesive composition comprising a therapeutical and/or health-promoting agent. For example, sumatriptan vaginal suppository were prepared from Suppocire AS2X, hydroxypropyl Me cellulose as a mucoadhesive agent, and Transcutol as a permeation enhancer.
- IT 19216-56-9, Prazosin 21256-18-8, Oxaprozin 63590-64-7, Terazosin 74191-85-8, Doxazosin 139264-17-8, Zolmitriptan
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)
- RN 19216-56-9 HCPLUS
- CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



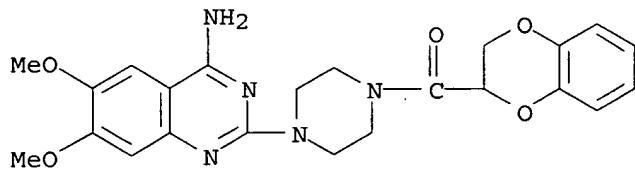
RN 21256-18-8 HCAPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)

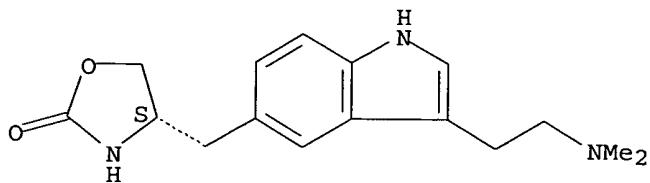


RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 139264-17-8 HCAPLUS
 CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L61 ANSWER 3 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:570428 HCAPLUS
 DOCUMENT NUMBER: 141:111615
 TITLE: Chronotherapy tablet and methods related thereto
 INVENTOR(S): Chopra, Sham
 PATENT ASSIGNEE(S): Can.
 SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S.
 Ser. No. 430,142.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004137062	A1	20040715	US 2003-697473	20031030
US 2003003151	A1	20030102	US 2002-85234	20020228 <--
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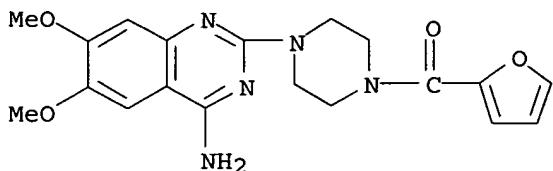
AB A chronotherapy tablet is provided for oral administration and the amelioration of at least one chronobiol. condition within 24 h comprising a substantially oblong core having a longitudinal axis, a first end and a second end, the core being comprised of at least two superposed layers of different compns. wherein an interface between each layer is substantially perpendicular to the longitudinal axis of the core and wherein at least one of the layers is a pharmacol. composition; a coating which envelops the core, except for at least one exposed release face of the core at at least one end of the core. Methods are provided for the prevention and/or treatment of asthma, arthritis (including, but not limited to, osteoarthritis and rheumatoid arthritis), gastrointestinal disorders, cardiovascular disease (including, but not limited to, hypertension, angina, myocardial infarction, and stroke), and cancer.

IT 19237-84-4, Prazosin hydrochloride 21256-18-8,
 Oxaprozin 63074-08-8, Terazosin hydrochloride
 77883-43-3, Doxazosin mesylate

RL: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);
 USES (Uses)
 (chronotherapy tablet and methods related thereto)

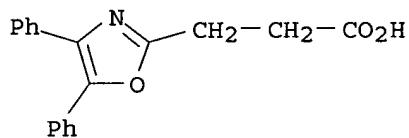
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CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride (9CI) (CA INDEX NAME)

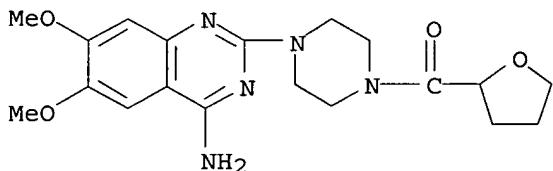


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 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63074-08-8 HCPLUS
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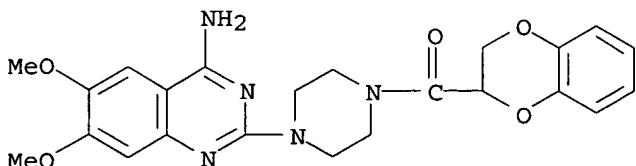


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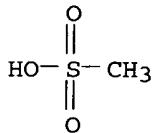
RN 77883-43-3 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8
 CMF C23 H25 N5 O5



CM 2

CRN 75-75-2
CMF C H4 O3 S

L61 ANSWER 4 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:430288 HCPLUS
 DOCUMENT NUMBER: 140:429017
 TITLE: Drug condensation aerosols and kits
 INVENTOR(S): Hale, Ron L.; Hodges, Craig C.; Lloyd, Peter M.; Lu, Amy T.; Myers, Daniel J.; Rabinowitz, Joshua D.; Wensley, Martin J.
 PATENT ASSIGNEE(S): Alexza Molecular Delivery Corporation, USA
 SOURCE: U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of U.S. Ser. No. 633,877.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 31
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US 2004099269	A1	20040527	US 2003-718982	20031120
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AB The present invention provides novel condensation aerosols for the treatment of disease and/or intermittent or acute conditions. These condensation aerosols have little or no pyrolysis degradation products and are characterized by having an MMAD of between 1-3 μ . The aerosols are made by rapidly heating a substrate coated with a thin film of drug having a thickness of between 0.05 and 20 μ m, while passing a gas over the film, to form particles of a desirable particle size for inhalation. Kits comprising a drug and a device for producing a condensation aerosol are also provided. The device contained in the kit typically, has an element for heating the drug which is coated as a film on the substrate and contains a therapeutically ED of a drug when the drug is administered in aerosol form, and an element allowing the vapor to cool to form an aerosol. Also disclosed, are methods for using these aerosols and kits. For example, acebutolol (MW 336, m.p. 123°, oral dose 400 mg), a β -adrenergic blocker (cardiovascular agent), was coated on a

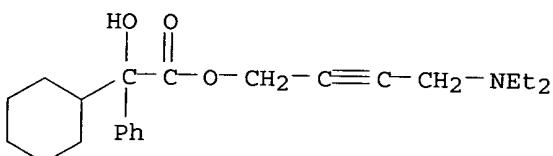
stainless steel cylinder (8 cm). The drug (0.89 mg) was applied to the substrate, for a calculated drug film thickness of 1.1 μm . The substrate was heated at 20.5 V and purity of the drug aerosol particles was determined to be 98.9%; 0.53 mg was recovered from the filter after vaporization, for a percent yield of 59.6%. A total mass of 0.81 mg was recovered from the test apparatus and substrate, for a total recovery of 91%. High speed photographs were taken as the drug-coated substrate was heated to monitor visually formation of a thermal vapor. The photographs showed that a thermal vapor was initially visible 30 ms after heating was initiated, with the majority of the thermal vapor formed by 130 ms. Generation of the thermal vapor was complete by 500 ms.

IT 5633-20-5, Oxybutynin 124937-51-5,
Tolterodine 139264-17-8, Zolmitriptan
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);
USES (Uses)

(drug condensation aerosols and kits for inhalation therapy)

RN 5633-20-5 HCPLUS

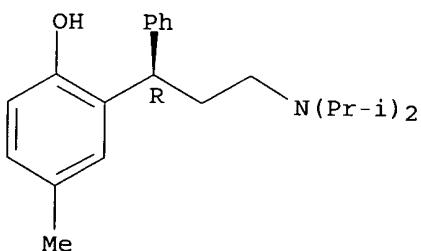
CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



RN 124937-51-5 HCPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-
(9CI) (CA INDEX NAME)

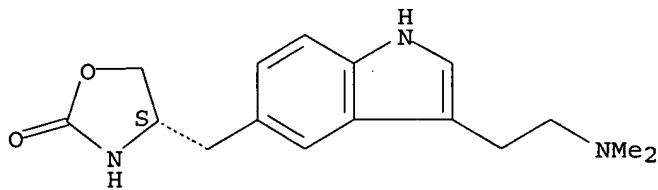
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RN 139264-17-8 HCPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-,
(4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L61 ANSWER 5 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:269853 HCAPLUS
DOCUMENT NUMBER: 140:309370
TITLE: Amino acid and peptide carriers for oral delivery of active agent
INVENTOR(S): Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence P.
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 176 pp., Cont.-in-part of U.S. Pat. Appl. 2002 128,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 20
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063628	A1	20040401	US 2002-156527	20020529
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WO	2004-US32131	A2	20040930

AB The present invention relates to oral delivery systems of active agent, and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for oral administration of conjugated active agent compns. For example, a polyserine-furosemide conjugate was prepared and its in vivo performance was examined. Compared to parent furosemide, the conjugate showed a sustained drug release. The 9 h serum level of the polyserine-furosemide conjugate was 95.5% of its 3 h level, whereas the 9 h serum level of the parent drug was only 59.8% of its 3 h level.

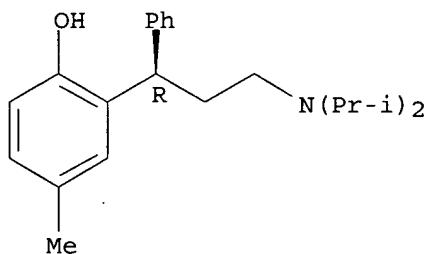
IT 124937-51-5DP, Tolterodine, conjugates with polyglutamic acid

RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates containing amino acid or peptide carriers for sustained-release oral drug delivery)

RN 124937-51-5 HCPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



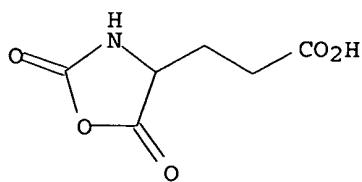
IT 33043-68-4 86409-29-2 137132-62-8

420824-40-4

RL: RCT (Reactant); RACT (Reactant or reagent)
(conjugates containing amino acid or peptide carriers for sustained-release oral drug delivery)

RN 33043-68-4 HCPLUS

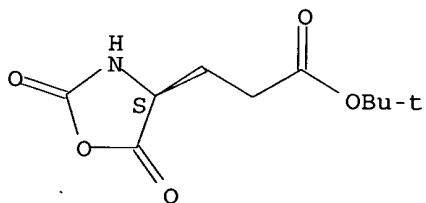
CN 4-Oxazolidinopropanoic acid, 2,5-dioxo-, (S)- (9CI) (CA INDEX NAME)



RN 86409-29-2 HCAPLUS

CN 4-Oxazolidinepropanoic acid, 2,5-dioxo-, 1,1-dimethylethyl ester, (4S)- (9CI) (CA INDEX NAME)

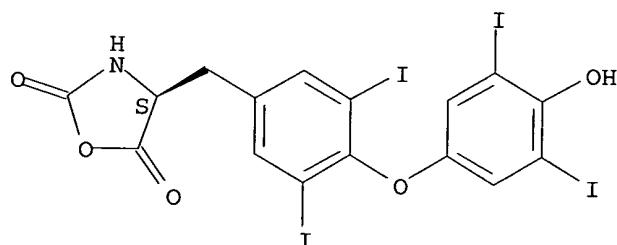
Absolute stereochemistry.



RN 137132-62-8 HCAPLUS

CN 2,5-Oxazolidinedione, 4-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]methyl-, (4S)- (9CI) (CA INDEX NAME)

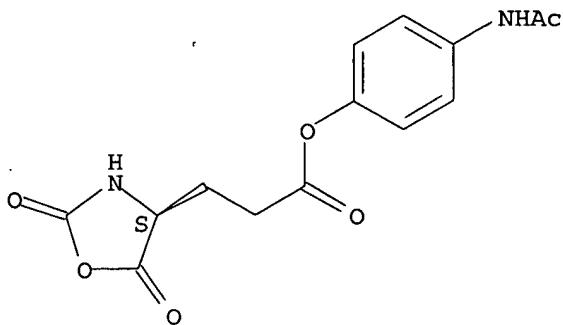
Absolute stereochemistry.



RN 420824-40-4 HCAPLUS

CN 4-Oxazolidinepropanoic acid, 2,5-dioxo-, 4-(acetylamino)phenyl ester, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

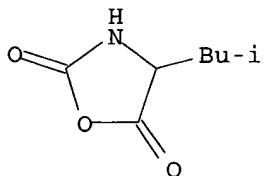


IT 3190-70-3P 3190-71-4P 14825-82-2P
 15776-11-1P 24601-74-9P 33043-58-2P
 33043-60-6P 45895-90-7P 420824-64-2P
 607706-94-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (conjugates containing amino acid or peptide carriers for sustained-release oral drug delivery)

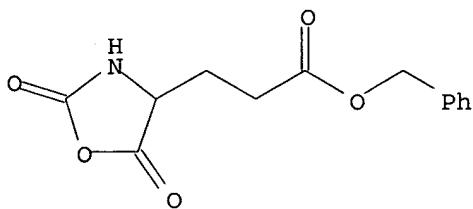
RN 3190-70-3 HCPLUS

CN 2,5-Oxazolidinedione, 4-(2-methylpropyl)-, (S)- (9CI) (CA INDEX NAME)



RN 3190-71-4 HCPLUS

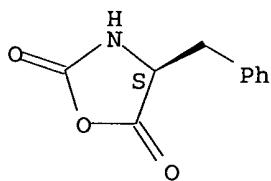
CN 4-Oxazolidinepropanoic acid, 2,5-dioxo-, phenylmethyl ester, (S)- (9CI) (CA INDEX NAME)



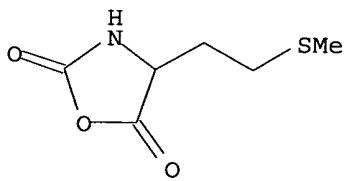
RN 14825-82-2 HCPLUS

CN 2,5-Oxazolidinedione, 4-(phenylmethyl)-, (4S)- (9CI) (CA INDEX NAME)

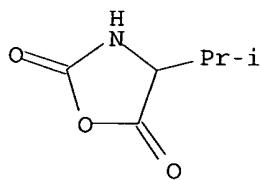
Absolute stereochemistry.



RN 15776-11-1 HCAPLUS
CN 2,5-Oxazolidinedione, 4-[2-(methylthio)ethyl]-, (S)- (9CI) (CA INDEX NAME)

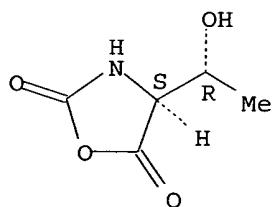


RN 24601-74-9 HCAPLUS
CN 2,5-Oxazolidinedione, 4-(1-methylethyl)-, (S)- (9CI) (CA INDEX NAME)



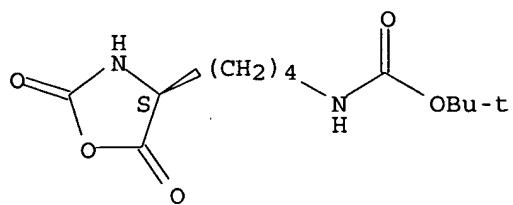
RN 33043-58-2 HCAPLUS
CN 2,5-Oxazolidinedione, 4-[(1R)-1-hydroxyethyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

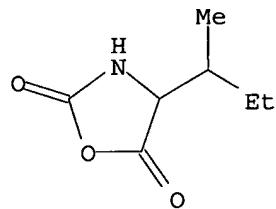


RN 33043-60-6 HCAPLUS
CN Carbamic acid, [4-[(4S)-2,5-dioxo-4-oxazolidinyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

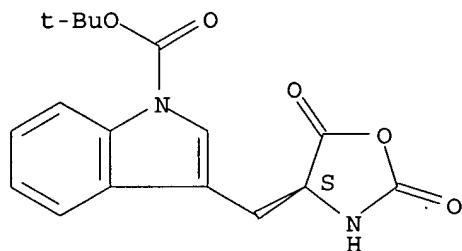


RN 45895-90-7 HCAPLUS
 CN 2,5-Oxazolidinedione, 4-(1-methylpropyl)-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)



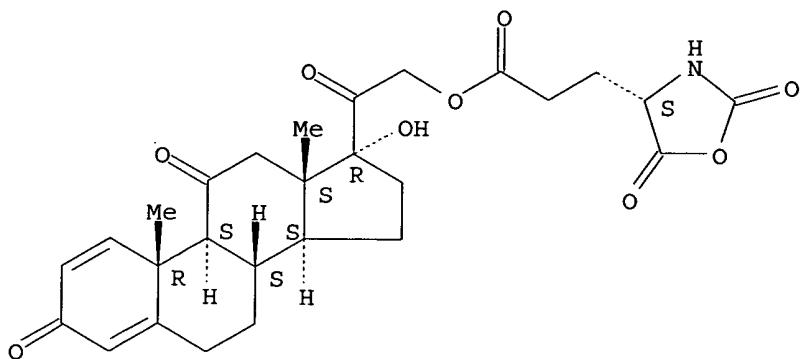
RN 420824-64-2 HCAPLUS
 CN 1H-Indole-1-carboxylic acid, 3-[[[(4S)-2,5-dioxo-4-oxazolidinyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 607706-94-5 HCAPLUS
 CN Pregna-1,4-diene-3,20-dione, 21-[4-[[[(4S)-2,5-dioxo-4-oxazolidinyl]oxy]-1-oxopropoxy]-11,17-dihydroxy-, (11β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L61 ANSWER 6 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:930970 HCPLUS

DOCUMENT NUMBER: 140:743

TITLE: Epoxy-steroidal aldosterone antagonist and calcium channel blocker combination therapy for treatment of cardiovascular disorders

INVENTOR(S): Schuh, Joseph R.

PATENT ASSIGNEE(S): G.D. Searle and Co., USA

SOURCE: U.S. Pat. Appl. Publ., 87 pp., Cont.-in-part of U.S. Ser. No. 126134, abandoned.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003220312	A1	20031127	US 2002-324330	20021219
US 2002132001	A1	20020919	US 2001-854264	20010511 <--
US 2002042405	A1	20020411	US 2001-917425	20010727 <--
US 2003055027	A1	20030320	US 2002-126134	20020419 <--
US 2005192259	A1	20050901	US 2005-121638	20050504
PRIORITY APPLN. INFO.:				
US 2000-203637P P 20000511				
US 2000-221359P P 20000727				
US 2001-854264 A1 20010511				
US 2001-917425 B1 20010727				
US 2002-126134 B2 20020419				

AB A combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a calcium channel blocker is described for treatment of circulatory disorders, including cardiovascular disorders such as hypertension, angina and congestive heart failure. Preferred calcium channel blockers are those compds. having high potency and bioavailability. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidals compds. characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. A preferred combination therapy includes the calcium channel blocker amlodipine and the aldosterone receptor antagonist eplerenone.

IT 104454-71-9, Ipenoxazone 129927-33-9, Temiverine hydrochloride

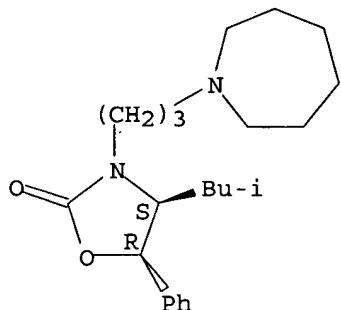
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blocker; epoxy-steroidal aldosterone antagonist and calcium channel blocker combination therapy for treatment of cardiovascular disorders)

RN 104454-71-9 HCPLUS

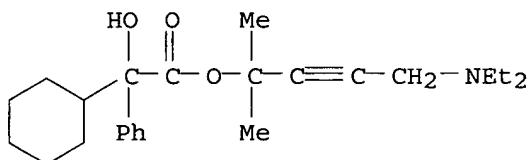
CN 2-Oxazolidinone, 3-[3-(hexahydro-1H-azepin-1-yl)propyl]-4-(2-methylpropyl)-5-phenyl-, (4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 129927-33-9 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L61 ANSWER 7 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:926825 HCPLUS

DOCUMENT NUMBER: 140:228444

TITLE: Quantitative relationship between rat intestinal absorption and Abraham descriptors

AUTHOR(S): Zhao, Yuan H.; Abraham, Michael H.; Hersey, Anne; Luscombe, Chris N.

CORPORATE SOURCE: Department of Chemistry, University College London, London, WC1H 0AJ, UK

SOURCE: European Journal of Medicinal Chemistry (2003), 38(11-12), 939-947

CODEN: EJMCA5; ISSN: 0223-5234

PUBLISHER: Elsevier Science Ltd.

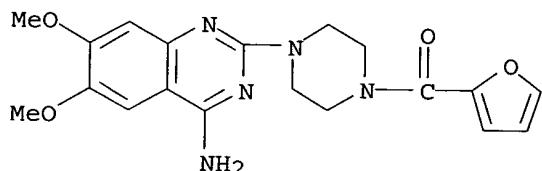
DOCUMENT TYPE: Journal

LANGUAGE: English

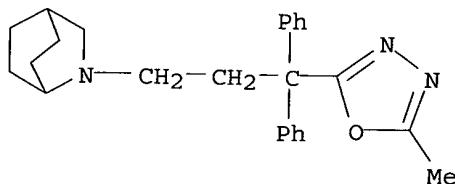
AB Literature data on the intestinal absorption of 158 drug and drug-like compds. in rats have been collected, and Abraham descriptors for the set of drugs have been calculated using the method of Platts and Abraham et al. Results show that there is a significant relationship between rat

intestinal absorption and the Abraham descriptors. In agreement with the human intestinal absorption model, the dominant descriptors in the rat model are the drug hydrogen bond acidity and basicity. In order to compare the absorption models in humans and rats, the absorption model developed from rats was used to predict the absorption in humans. The rat intestinal absorption model is similar to the human absorption model, and data on rats can effectively be used to predict human intestinal absorption.

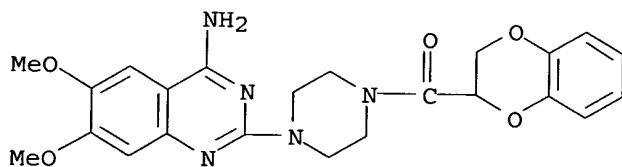
- IT 19216-56-9, Prazosin 57726-65-5, Nufenoxole
 74191-85-8, Doxazosin 106133-20-4,
 Tamsulosin
 RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (quant. structure-activity relationship (QSAR) between rat intestinal drug absorption and Abraham descriptors)
- RN 19216-56-9 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



- RN 57726-65-5 HCPLUS
 CN 2-Azabicyclo[2.2.2]octane, 2-[3-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3-diphenylpropyl]- (9CI) (CA INDEX NAME)

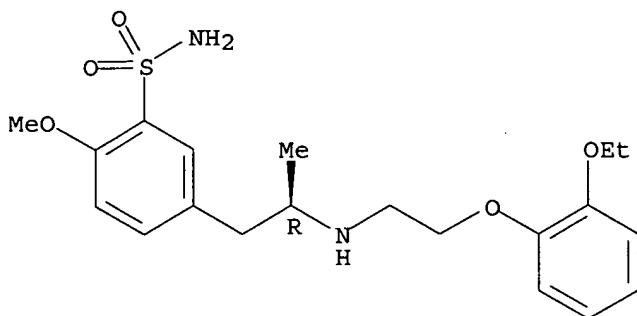


- RN 74191-85-8 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



- RN 106133-20-4 HCPLUS
 CN Benzenesulfonamide, 5-[(2R)-2-[(2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 8 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:726750 HCPLUS

DOCUMENT NUMBER: 139:333072

TITLE: Identification and prediction of promiscuous aggregating inhibitors among known drugs

AUTHOR(S): Seidler, James; McGovern, Susan L.; Doman, Thompson N.; Shoichet, Brian K.

CORPORATE SOURCE: Department of Molecular Pharmacology and Biological Chemistry, Northwestern University, Chicago, IL, 60611, USA

SOURCE: Journal of Medicinal Chemistry (2003), 46(21), 4477-4486

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

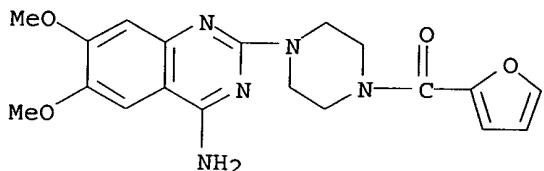
LANGUAGE: English

AB Some small mols., often hits from screening, form aggregates in solution that inhibit many enzymes. In contrast, drugs are thought to act specifically. To investigate this assumption, 50 unrelated drugs were tested for promiscuous inhibition via aggregation. Each drug was tested against three unrelated model enzymes: β -lactamase, chymotrypsin, and malate dehydrogenase, none of which are considered targets of these drugs. To be judged promiscuous, the drugs had to inhibit all three enzymes, do so in a time-dependent manner, be sensitive to detergent and to enzyme concentration,

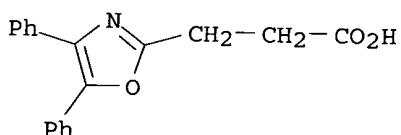
and

form particles detectable by light scattering. Of the 50 drugs tested, 43 were nonpromiscuous by these criteria. Surprisingly, four of the drugs showed promiscuous, aggregation-based inhibition at concns. below 100 μ M: clotrimazole, benzyl benzoate, nicardipine, and delavirdine. Three other drugs also behaved as aggregation-based inhibitors, but only at high concns. (about 400 μ M). To investigate possible structure-activity relationships among promiscuous drugs, five analogs of the antifungal clotrimazole were studied. Three of these, miconazole, econazole, and sulconazole, were promiscuous but the other two, fluconazole and ketoconazole, were not. Using recursive partitioning, these exptl. results were used to develop a model for predicting aggregate-based promiscuity. This model correctly classified 94% of 111 compds.-- 47 aggregators and 64 nonaggregators-- that have been studied for this effect. To evaluate the model, it was used to predict the behavior of 75 drugs not previously investigated for aggregation. Several preliminary points emerge. Most drugs are not promiscuous, even at high concns. Nevertheless, at high enough concns. (20-400 μ M), some drugs can aggregate and act promiscuously, suggesting that aggregation may be common

IT among small mols. at micromolar concns., at least in biochem. buffers.
 19216-56-9, Prazosin 21256-18-8, Oxaprozin
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); BIOL (Biological study); PROC (Process)
 (identification and prediction of promiscuous aggregating enzyme inhibitors among known drugs)
 RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 21256-18-8 HCAPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

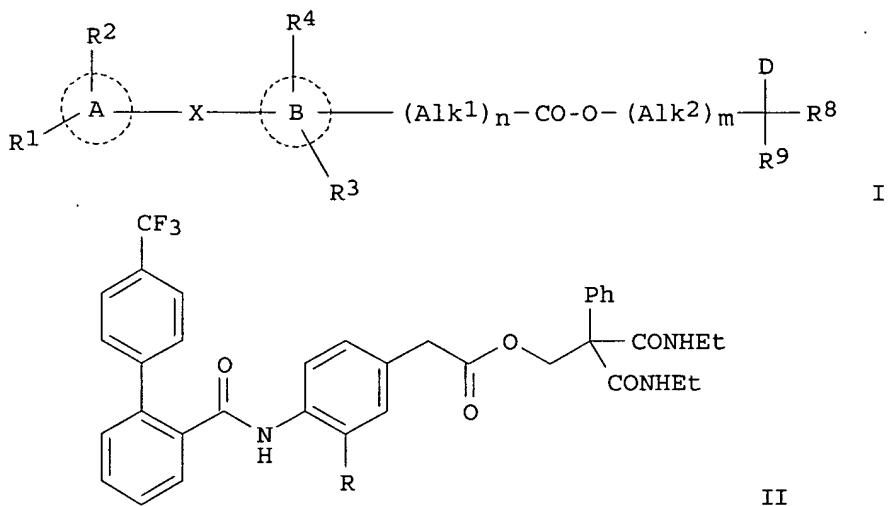
L61 ANSWER 9 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:696857 HCAPLUS
 DOCUMENT NUMBER: 139:230479
 TITLE: Preparation of [4-(1,1'-biphenyl-2-ylcarbonylamino or benzoylamino)phenyl]acetic acid esters as microsomal triglyceride transfer protein (MTP) inhibitors
 INVENTOR(S): Hagiwara, Atsushi; Oe, Yasuhiro; Odani, Naoya; Watanabe, Shizue; Ikenogami, Taku; Kawai, Takashi; Madono, Kenya; Taniguchi, Toshio
 PATENT ASSIGNEE(S): Japan Tobacco Inc., Japan
 SOURCE: PCT Int. Appl., 561 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072532	A1	20030904	WO 2003-JP2398	20030228 <--
W:	AE, AG, AL, AM, AU, AZ, BA, BB, BR, BY, BZ, CA, CN, CO, CR, CU, DM, DZ, EC, GD, GE, HR, ID, IL, IN, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, RU, SC, SG, TJ, TM, TN, TT, UA, US, UZ, VC, VN, YU, ZA			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,			

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 CA 2460682 AA 20030904 CA 2003-2460682 20030228 <--
 AU 2003211617 A1 20030909 AU 2003-211617 20030228 <--
 JP 2003321424 A2 20031111 JP 2003-53869 20030228
 JP 3662566 B2 20050622
 BR 2003006292 A 20040824 BR 2003-6292 20030228
 EP 1479666 A1 20041124 EP 2003-743078 20030228
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 CN 1630629 A 20050622 CN 2003-804734 20030228
 ZA 2005002495 A 20050920 ZA 2005-2495 20030228
 ZA 2005002496 A 20051012 ZA 2005-2496 20030228
 NZ 531890 A 20060224 NZ 2003-531890 20030228
 ZA 2004002275 A 20050423 ZA 2004-2275 20040323
 NO 2004001872 A 20040506 NO 2004-1872 20040506
 US 2005075367 A1 20050407 US 2004-492831 20041008
 JP 2005194281 A2 20050721 JP 2005-19579 20050127
 JP 2005220132 A2 20050818 JP 2005-19739 20050127
 JP 2005220133 A2 20050818 JP 2005-20179 20050127
 AU 2005248950 A1 20060119 AU 2005-248950 20051223
 PRIORITY APPLN. INFO.: JP 2002-53876 A 20020228
 GI AU 2003-211617 A3 20030228
 JP 2003-53869 A3 20030228
 WO 2003-JP2398 W 20030228

OTHER SOURCE(S): MARPAT 139:230479

GI



AB The title compds. [I; R1, R2 = H, C1-6 alkyl, C3-7 cycloalkyl, C1-6 alkoxy, halo-C1-6 alkyl, halo-C1-6 alkoxy, each (un)substituted C6-14 aryl, C7-16 aralkyl, C6-14 aryloxy, C7-16 aryloxy, C7-16 aralkyloxy, C7-15 arylcarbonyl, heterocyclyl, or NH2 C2-7 alkoxycarbonyl, halo, C2-6 alkenyl; the ring A = C6-14 aryl, heterocyclyl, 9-oxofluorenyl, fluorenyl; X = CO2(CH2)n, each N-(un)substituted CONH(CH2)n or NHCO(CH2)n (wherein n = an integer of 0-3); R3, R4 = H, HO, halo, each (un)substituted C1-6 alkyl, heterocyclyl, or CONH2, C1-6 alkoxy, halo-C1-6 alkyl, C7-16 aralkyloxy, C1-6 acyl; the ring B = phenylene, C5-7 (aza)cycloalkanediyl, indolediyl, benzimidazolediyl, pyridinediyl, pyrimidinediyl,

benzocycloalkanediyl, quinolinediyl, etc.; Alk11, Alk12 = alkanediyl, alkenediyl; n, m = 0-3; D = C1-6 alkyl, C2-6 alkenyl, C2-7 alkoxy carbonyl, NR42COR43 (wherein R42 = H, C1-6 alkyl; R43 = C4-14 aryl, C7-16 aralkyl), etc.; R8, R9 = H, C1-6 alkyl, (un)substituted C6-14 aryl, CONH₂, or NH₂, succinimid-2-yl, hydroxy-C1-6 alkyl, CO₂H or its ester, (CH₂)_sO₂CR20 (wherein R20 = H, C1-6 alkyl, C3-7 cycloalkyl; s = 0-3)] or prodrugs thereof or pharmaceutically acceptable salts of either are prepared. These compds. I electively inhibit microsomal triglyceride transfer protein (MTP) of small intestine, are metabolized in blood or liver, and residual amount of MTP inhibitors is small enough not to substantially inhibit liver MTP and hence causes no side effects such as a fatty liver. They are useful for prevention or treatment of hyperlipidemia, arteriosclerosis, coronary artery diseases, obesity, diabetes, or hypertension. Thus, 519 mg 4-[(4'-trifluoromethyl-1,1'-biphenyl-2-ylcarbonyl)amino]phenylacetic acid (preparation given), 317 mg 2-hydroxymethyl-2-phenylmalonic acid diethylamide pg, and 268 mg 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were dissolved in 5 mL CH₂Cl₂ and stirred at room temperature for 6 h to give, after distillation of the solvent and silica gel chromatog., 725 mg

4-[(4'-trifluoromethyl-1,1'-biphenyl-2-ylcarbonyl)amino]phenylacetic acid 2,2-bis(ethylcarbamoyl)-2-phenylethyl ester (II; R = H). II (R = H) and II (R = Me) inhibited the triglyceride transport between liposomes by MTP with IC₅₀ of 0.6 and 0.39 nM, resp., and the secretion of apolipoprotein B from HepG2 cell with IC₅₀ of 0.65 and 0.46, resp. Pharmaceutical formulations, e.g. a tablet containing 2-[[2-[4-[(4'-trifluoromethyl-1,1'-biphenyl-2-ylcarbonyl)amino]-3-(pyrrolidinocarbonyl)phenyl]acetoxy]methyl]-2-phenylmalonic acid di-Et ester, were described.

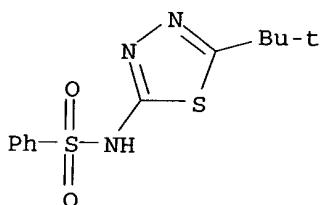
IT 1492-02-0, Glybzole

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antidiabetic agent, coadministration drugs containing; preparation of [(biphenylylcarbonylamino or benzoylamino)phenyl]acetic acid esters as microsomal triglyceride transfer protein (MTP) inhibitors for treatment or prevention of diseases)

RN 1492-02-0 HCPLUS

CN Benzenesulfonamide, N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl] - (9CI) (CA INDEX NAME)



IT 19237-84-4, Prazosin hydrochloride 63074-08-8, Terazosin hydrochloride 77883-43-3, Doxazosin mesylate

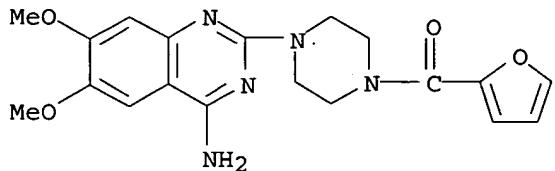
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antihypertensive agent, coadministration drugs containing; preparation of [(biphenylylcarbonylamino or benzoylamino)phenyl]acetic acid esters as microsomal triglyceride transfer protein (MTP) inhibitors for treatment or prevention of diseases)

RN 19237-84-4 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-

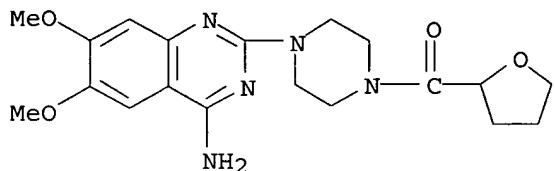
, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 63074-08-8 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

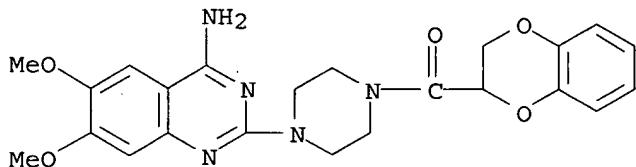
RN 77883-43-3 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8

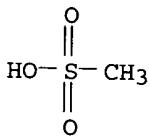
CMF C23 H25 N5 O5



CM 2

CRN 75-75-2

CMF C H4 O3 S



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 10 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:610237 HCPLUS
 DOCUMENT NUMBER: 139:154928
 TITLE: Multi-stage oral controlled-release drug delivery systems
 INVENTOR(S): Park, Jin Woo; Bae, Joon Ho; Kim, Jung Ju
 PATENT ASSIGNEE(S): Pacific Corporation, S. Korea
 SOURCE: PCT Int. Appl., 47 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003063834	A1	20030807	WO 2003-KR200	20030129 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
KR 2003066351	A	20030809	KR 2003-5153	20030127 <--
CA 2472237	AA	20030807	CA 2003-2472237	20030129 <--
EP 1469834	A1	20041027	EP 2003-705420	20030129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1625390	A	20050608	CN 2003-803154	20030129
JP 2005526019	T2	20050902	JP 2003-563528	20030129
US 2003180362	A1	20030925	US 2003-357821	20030203 <--
PRIORITY APPLN. INFO.:			KR 2002-5858	A 20020201
			WO 2003-KR200	W 20030129

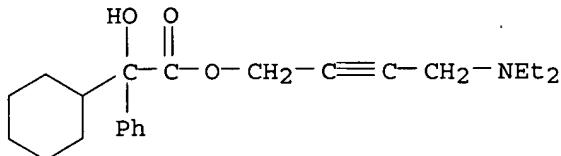
AB The present invention relates to, as a novel oral drug delivery system for control of drug release, a preparation for maintaining drug concentration in blood at

a certain level for a prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation. Compns. of core matrix tablets contained captorpril 25, glyceryl behenate 62.5, dibasic calcium phosphate dihydrate 5, Povidone 5, hydroxypropyl Me cellulose 150, and Mg stearate 2.5 mg, and moisture (removed during treatment) and the coating solution comprised hydroxypropyl Me cellulose 9.6, Et cellulose 2.4, methylene chloride 93.4, EtOH 93.4, and castor oil 1.2%.

IT 1508-65-2, Oxybutynin hydrochloride 5633-20-5,

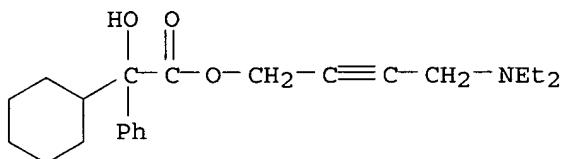
Oxybutynin 21256-18-8, Oxaprozin 74191-85-8,
 Doxazosin 124937-51-5, Tolterodine
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (multi-stage oral controlled-release drug delivery systems)

RN 1508-65-2 HCPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)

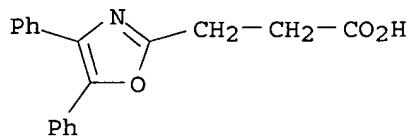


● HCl

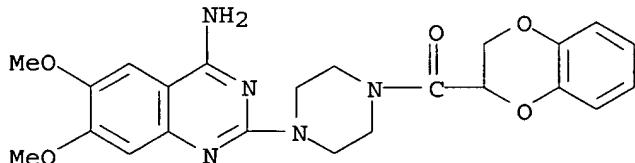
RN 5633-20-5 HCPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



RN 21256-18-8 HCPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



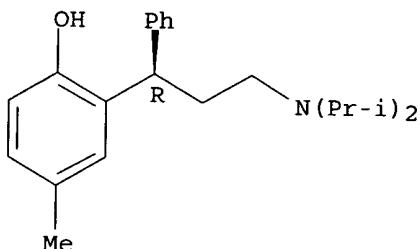
RN 74191-85-8 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 124937-51-5 HCPLUS
 CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-

(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 11 OF 77 HCAPLUS .COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:477919 HCAPLUS

DOCUMENT NUMBER: 139:358004

TITLE: A hierarchical QSAR model for urinary excretion of drugs in humans as a predictive tool for biotransformation

AUTHOR(S): Manga, Na'ngono; Duffy, Judith C.; Rowe, Philip H.; Cronin, Mark T. D.

CORPORATE SOURCE: School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, L3 3AF, UK

SOURCE: QSAR & Combinatorial Science (2003), 22(2), 263-273

PUBLISHER: CODEN: QCSSAU; ISSN: 1611-020X

DOCUMENT TYPE: Wiley-VCH Verlag GmbH & Co. KGaA

LANGUAGE: English

AB Of the many pharmacokinetic endpoints applicable to in silico screening, drug biotransformation seen as a hybrid, multi-enzymic disposition parameter, was little addressed. The aim of this study was to model drug biotransformation, utilizing metabolism data for a heterogeneous group of drugs. The data were the cumulative amount of unchanged drug excreted in the urine, expressed as percent of the i.v. dose, administered for 160 drugs. The data were categorized into classes according to excretion ranges. The cut-off values between those ranges were defined so as to enable optimal modeling. For each drug, a total of 72 physiochem. and structural descriptors were calculated. Modeling of the drug metabolism data was

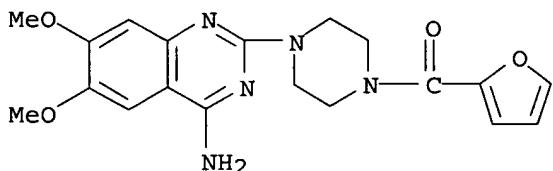
attempted utilizing a hierarchical approach comprising a set of rules combining both linear discriminant anal. and recursive partitioning. The model developed into a decision tree involving the following descriptors: LogD6.5, counts of H-bond donors, ionization potential, COSMIC total energy, electronic energy, counts of OH-groups and COOH-groups and the sum of the total net charges. Overall, this model assigned 90% of the compds. correctly to the categories of extensively, or non-extensively, metabolized. The model was successfully validated using an external test set of 40 compds.

IT 19216-56-9, Prazosin 21256-18-8, Oxaprozin
63590-64-7, Terazosin

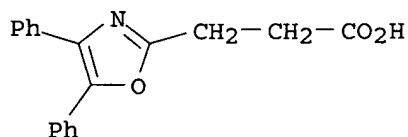
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(hierarchical QSAR model for urinary excretion of drugs in humans as predictive tool for biotransformation)

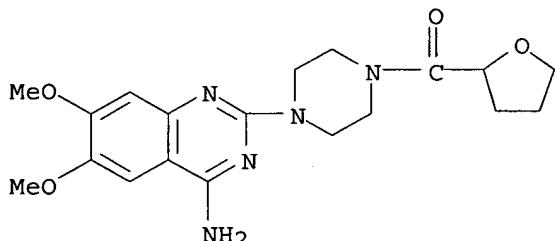
RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 21256-18-8 HCAPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 12 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:459731 HCAPLUS
 DOCUMENT NUMBER: 139:122572
 TITLE: Molecular Descriptors Influencing Melting Point and Their Role in Classification of Solid Drugs
 AUTHOR(S): Bergstroem, Christel A. S.; Norinder, Ulf; Luthman, Kristina; Artursson, Per
 CORPORATE SOURCE: Center of Pharmaceutical Informatics, Department of Pharmacy, Uppsala University, Uppsala, SE-751 23, Swed.
 SOURCE: Journal of Chemical Information and Computer Sciences (2003), 43(4), 1177-1185
 CODEN: JCISD8; ISSN: 0095-2338
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The aim of the study was to investigate whether easily and rapidly calculated

2D and 3D mol. descriptors could predict the m.p. of drug-like compds., to allow a m.p. classification of solid drugs. The m.ps. for 277 structurally diverse model drugs were extracted from the 12th edition of the Merck Index. 2D descriptors mainly representing electropotol. and electron accessibilities were calculated by Molconn-Z and the AstraZeneca inhouse program Selma. 3D descriptors for mol. surface areas were generated using the programs MacroModel and Marea. Correlations between the calculated descriptors and the m.p. values were established with partial least squares projection to latent structures (PLS) using training and test sets. Three different descriptor matrixes were studied, and the models obtained were used for consensus modeling. The calculated properties were shown to explain 63% of the m.p. Descriptors for hydrophilicity, polarity, partial atom charge, and mol. rigidity were found to be pos. correlated with m.p., whereas nonpolar atoms and high flexibility within the mol. were neg. correlated to this solid-state characteristic. Moreover, the studied descriptors were successful in providing a qual. ranking of compds. into classes displaying a low, intermediate, or high m.p. Finally, a mechanism for the relation between the mol. descriptors and their effect on the m.p. and the aqueous solubility was proposed.

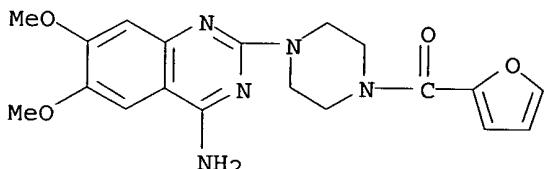
IT 19216-56-9, Prazosin 21256-18-8, Oxaprozin

RL: PRP (Properties)

(mol. descriptors influencing m.p. and their role in classification of solid drugs)

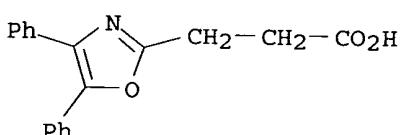
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



RN 21256-18-8 HCAPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 13 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:334829 HCAPLUS

DOCUMENT NUMBER: 138:343889

TITLE: Novel pharmaceutical compounds containing drugs bound to polypeptides

INVENTOR(S): Picariello, Thomas

PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA

SOURCE: PCT Int. Appl., 4662 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 20

PATENT INFORMATION:

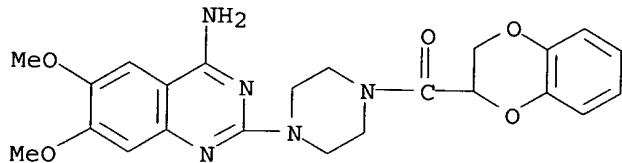
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003034980	A2	20030501	WO 2001-US43089	20011114 <--
WO 2003034980	C1	20031120		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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EP 1401374	A1	20040331	EP 2001-274606	20011114
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JP 2006516948	T2	20060713	JP 2003-537549	20011114
US 2004063628	A1	20040401	US 2002-156527	20020529
US 7060708	B2	20060613		

PRIORITY APPLN. INFO.:

US 2000-274622P	P 20001114
US 1999-265415	B2 19990310
US 1999-411238	B2 19991004
WO 2000-US5693	A 20000306
US 2000-642820	A2 20000822
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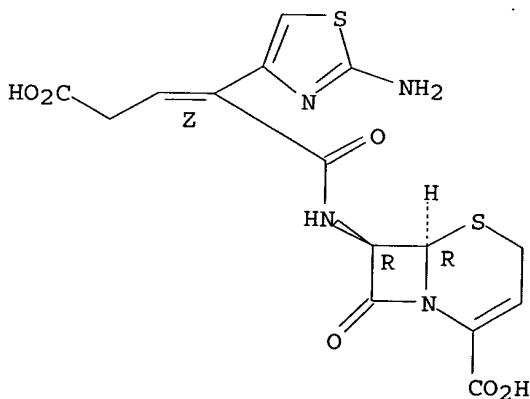
US 2001-986426	A2 20011108
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WO 2001-US43089	W 20011114
US 2001-988034	B2 20011116
US 2001-988071	B2 20011116
WO 2001-US43115	B2 20011116
WO 2001-US43117	B2 20011116
US 2002-358381P	P 20020222
US 2002-366258P	P 20020322

- AB Compns. comprising polypeptides and drugs covalently attached to the polypeptide are disclosed. Also provided is a method for delivery of these drugs to a patient comprising administering to the patient a composition comprising a polypeptide and a drug covalently attached to the polypeptide. Also provided is a method for protecting drugs from degradation comprising covalently attaching them to a polypeptide. Also provided is a method for controlling release of drugs from a composition comprising covalently attaching them to the polypeptide.
- IT 74191-85-8DP, Doxazosin, protein conjugates
 97519-39-6DP, Ceftibuten, protein conjugates
 RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (novel pharmaceutical compds. containing drugs bound to polypeptides)
- RN 74191-85-8 HCAPLUS
- CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



- RN 97519-39-6 HCAPLUS
- CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 7-[[[(2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-,
 (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



L61 ANSWER 14 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:300530 HCAPLUS
 DOCUMENT NUMBER: 138:314620
 TITLE: Calcium channel multibinding drugs, and uses
 INVENTOR(S): Ji, Yu-Hua; Natarajan, Maya; Griffin, John H.;
 Jenkins, Thomas E.
 PATENT ASSIGNEE(S): Theravance, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 183 pp., Cont.-in-part of U.S.
 Ser. No. 325,557, abandoned.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 31
 PATENT INFORMATION:

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US 2003073127	A1	20030417	US 1999-456429	19991208 <--
US 6897305	B2	20050524		
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CA 2319142	AA	19991216	CA 1999-2319142	19990607 <--
CA 2319153	AA	19991216	CA 1999-2319153	19990607 <--
WO 9963984	A1	19991216	WO 1999-US11801	19990607 <--
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AU 9945511	A1	19991230	AU 1999-45511	19990607 <--
AU 9946726	A1	19991230	AU 1999-46726	19990607 <--
AU 9946726	A	19991230		
EP 1085879	A2	20010328	EP 1999-928442	19990607 <--
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EP 1085890	A1	20010328	EP 1999-930122	19990607 <--
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EP 1089749	A1	20010411	EP 1999-928447	19990607 <--
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JP 2002517437	T2	20020618	JP 2000-553053	19990607 <--
ZA 2000004562	A	20011130	ZA 2000-4562	20000831 <--
ZA 2000004563	A	20011130	ZA 2000-4563	20000831 <--
ZA 2000004564	A	20011130	ZA 2000-4564	20000831 <--
US 2003044845	A1	20030306	US 2002-75017	20020213 <--
US 2004242561	A1	20041202	US 2004-877368	20040625
PRIORITY APPLN. INFO.:				
			US 1998-88465P	P 19980608
			US 1998-93068P	P 19980716
			US 1998-103866P	P 19981012
			US 1999-325557	B2 19990604
			US 1999-327096	B1 19990607
			WO 1999-US11801	W 19990607
			WO 1999-US12724	W 19990607
			WO 1999-US12754	W 19990607
			US 1999-456429	A1 19991208
			US 2000-499176	B1 20000207

OTHER SOURCE(S): MARPAT 138:314620

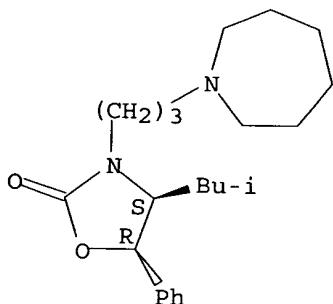
AB Multibinding compds. are disclosed. The compds. of the invention comprise 2-10 ligands covalently connected via linker groups, each of the ligands being capable of binding to a ligand-binding site in a calcium channel, thereby modulating the biol. activities thereof. The compds. of the invention may be used to treat diseases or conditions resulting from calcium channel activity. Pharmaceutical compns. are also disclosed.

IT 104454-71-9D, Ipenoxazone, ligand-linker conjugates
 173324-94-2D, Temiverine, ligand-linker conjugates
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (calcium channel multibinding drugs, and uses)

RN 104454-71-9 HCPLUS

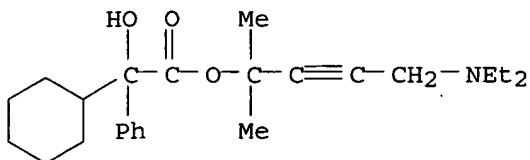
CN 2-Oxazolidinone, 3-[3-(hexahydro-1H-azepin-1-yl)propyl]-4-(2-methylpropyl)-5-phenyl-, (4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 173324-94-2 HCPLUS

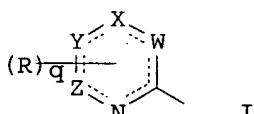
CN Benzeneacetic acid, α-cyclohexyl-α-hydroxy-,
 4-(diethylamino)-1,1-dimethyl-2-butynyl ester (9CI) (CA INDEX NAME)



L61 ANSWER 15 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:222367 HCAPLUS
 DOCUMENT NUMBER: 138:238175
 TITLE: Preparation of heterocyclic compounds as metabotropic glutamate receptor 5 (mGluR5) modulators
 INVENTOR(S): Cosford, Nicholas David Peter; Bleicher, Leo Solomon; Vernier, Jean-Michel Andre; Cube, Rowena V.; Schweiger, Edwin J.; McDonald, Ian
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Ser. No. 387,073, abandoned.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003055247	A1	20030320	US 2002-217800	20020813 <-
US 6774138	B2	20040810		
US 2005043307	A1	20050224	US 2004-874835	20040623
US 2005085523	A1	20050421	US 2004-874991	20040623
US 2005245542	A1	20051103	US 2005-97047	20050401
PRIORITY APPLN. INFO.:			US 1999-387073	B2 19990831
			US 2002-217800	A2 20020813
			US 2004-874835	A2 20040623

OTHER SOURCE(S): MARPAT 138:238175
 GI



AB The title compds. with general formula of A-L-B [wherein A = 5-7 membered ring I (where at least one of W, X, Y, and Z = (CR)p; p = 0-2; and the remainder of W, X, Y, and Z = independently O, N, S; R = halo, SH, NO2, CO2H, carbamate, carboxamide, OH, ester, CN, NH2, amide, amidine, amido, SO2, (un)substituted hydrocarbyl, aryl, or heterocyclyl); q = 0-3; L = (un)substituted alkenylene, alkynylene, or azo; B = (un)substituted (cyclo)hydrocarbyl, heterocyclyl, or aryl] and enantiomers, diastereomers, mixts., or their pharmaceutically acceptable salts thereof, which are capable of modulating the activity of excitatory amino acid receptors such as metabotropic glutamate receptor, are prepared Thus, reacting 2-bromo-1,3-thiazole with phenylacetylene in the presence of CuI, Et3N, and PdCl2(PPh3)2 in DME, followed by treatment of the resulting

IT 2-(phenylethyynyl)-1,3-thiazole with p-TsOH afforded 2-(phenylethyynyl)-1,3-thiazole, p-TsOH salt.

IT 329202-84-8P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of heterocyclic compds. as metabotropic glutamate receptor 5 (mGluR5) modulators)

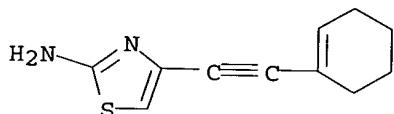
RN 329202-84-8 HCAPLUS

CN 2-Thiazolamine, 4-(1-cyclohexen-1-ylethyynyl)-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 329202-83-7

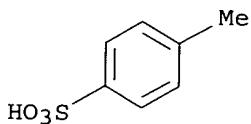
CMF C11 H12 N2 S



CM 2

CRN 104-15-4

CMF C7 H8 O3 S

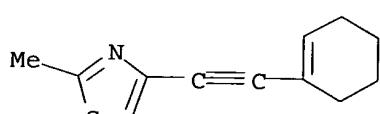


IT 329202-79-1P 329202-80-4P 329202-83-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic compds. as metabotropic glutamate receptor 5 (mGluR5) modulators)

RN 329202-79-1 HCAPLUS

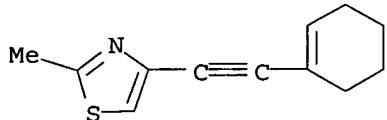
CN Thiazole, 4-(1-cyclohexen-1-ylethyynyl)-2-methyl- (9CI) (CA INDEX NAME)



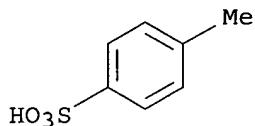
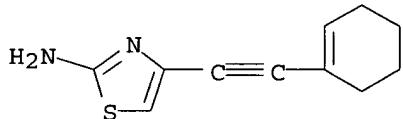
RN 329202-80-4 HCAPLUS

CN Thiazole, 4-(1-cyclohexen-1-ylethyynyl)-2-methyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 329202-79-1
CMF C12 H13 N S

CM 2

CRN 104-15-4
CMF C7 H8 O3 SRN 329202-83-7 HCPLUS
CN 2-Thiazolamine, 4-(1-cyclohexen-1-yethynyl)- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 16 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:202410 HCPLUS
 DOCUMENT NUMBER: 138:226705
 TITLE: Novel pharmaceuticals comprising drug conjugates with polypeptide carriers
 INVENTOR(S): Picariello, Thomas
 PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
 SOURCE: PCT Int. Appl., 2059 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 20
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2003020200	A2	20030313	WO 2001-US43117	20011116 <--
WO 2003020200	A3	20030912		

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 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
 UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
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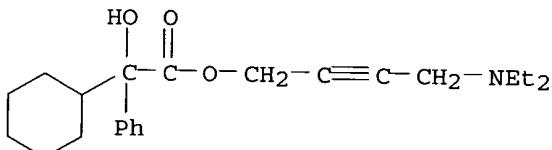
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JP 2006516947	T2	20060713	JP 2003-524514	20011116
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PRIORITY APPLN. INFO.:	US 2000-248600P	P 20001116
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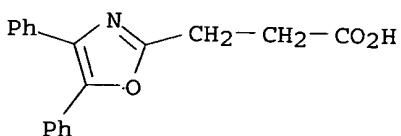
US 2001-248781P	P 20011116
US 2001-248783P	P 20011116
US 2001-248784P	P 20011116
US 2001-248785P	P 20011116
US 2001-248786P	P 20011116
US 2001-248787P	P 20011116
US 2001-248790P	P 20011116
US 2001-248791P	P 20011116
US 2001-248792P	P 20011116
US 2001-248793P	P 20011116
US 2001-248833P	P 20011116
US 2001-248848P	P 20011116
US 2001-248849P	P 20011116
US 2001-988034	B2 20011116
US 2001-988071	B2 20011116
WO 2001-US43115	B2 20011116
WO 2001-US43117	W 20011116
US 2002-358381P	P 20020222
US 2002-366258P	P 20020322

- AB A pharmaceutical composition comprising a polypeptide and an active agent attached to said polypeptide is disclosed.
- IT 1508-65-2D, Oxybutynin chloride, polypeptide conjugates
 21256-18-8D, Oxaprozin, polypeptide conjugates 63590-64-7D,
 , Terazosin, polypeptide conjugates 106133-20-4D,
 Tamsulosin, polypeptide conjugates 124937-51-5D,
 Tolterodine, polypeptide conjugates 139264-17-8D,
 Zolmitriptan, polypeptide conjugates
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (novel pharmaceuticals comprising drug conjugates
 with polypeptide carriers)
- RN 1508-65-2 HCPLUS
- CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)



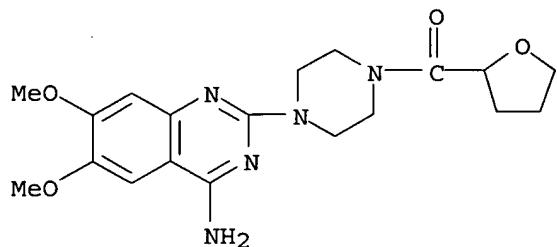
● HCl

- RN 21256-18-8 HCPLUS
- CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



- RN 63590-64-7 HCPLUS
- CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-

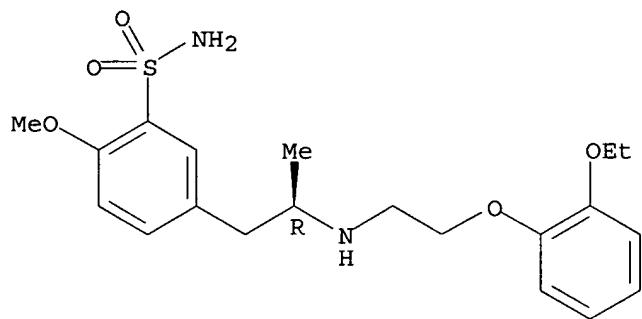
furanyl) carbonyl] - (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[(2-(2-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

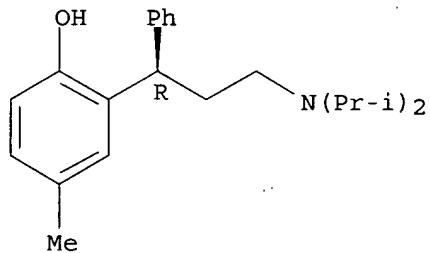
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCAPLUS

CN Phenol, 2-[(1R)-3-[(2S)-2-[(4-methoxyphenyl)methyl]amino]propyl]-4-methyl- (9CI) (CA INDEX NAME)

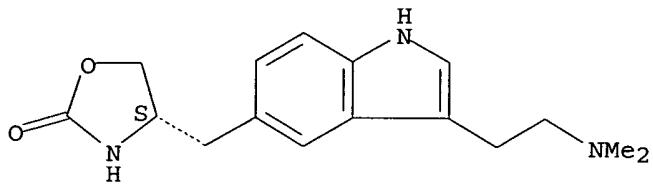
Absolute stereochemistry. Rotation (+).



RN 139264-17-8 HCAPLUS

CN 2-Oxazolidinone, 4-[(3-[(2S)-2-[(dimethylamino)ethyl]indol-5-yl]methyl)- (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L61 ANSWER 17 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:977687 HCAPLUS
 DOCUMENT NUMBER: 138:61310
 TITLE: Medicinal compositions containing drugs, drug absorption enhancers, and taurine compounds or polyamines
 INVENTOR(S): Kimura, Toshikiro; Higaki, Kazutaka; Miyake, Masateru; Minami, Takanori
 PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 64 pp.
 CODEN: PIIXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102414	A1	20021227	WO 2002-JP5954	20020614 <--
W: AU, CA, CN, KR, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
CA 2449952	AA	20021227	CA 2002-2449952	20020614 <--
JP 2003063997	A2	20030305	JP 2002-174289	20020614 <--
EP 1407785	A1	20040414	EP 2002-738715	20020614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
CN 1518461	A	20040804	CN 2002-811869	20020614
JP 2003171313	A2	20030620	JP 2002-285238	20020930 <--
US 2004161407	A1	20040819	US 2003-480598	20031212
US 6884768	B2	20050426		
US 2005095290	A1	20050505	US 2004-11035	20041215
US 7008920	B2	20060307		
US 2005100530	A1	20050512	US 2004-11278	20041215
PRIORITY APPLN. INFO.:			JP 2001-180373	A 20010614
			JP 2001-298839	A 20010928
			WO 2002-JP5954	W 20020614
			US 2003-480598	A3 20031212

AB Disclosed are medicinal compns. containing (1) a pharmacol. active substance, (2) a drug sorbefacient, and (3) a taurine compound or a polyamine. A taurine compound has an effect of lessening or preventing injuries on the intestinal mucosa. By adding the taurine compound to medicinal compns. containing a pharmacol. active substance and a drug sorbefacient, therefore, injuries on the intestinal mucosa due to the drug sorbefacient can be lessened or prevented. A polyamine has an effect of improving the absorbability of a pharmacol. active substance. By adding the polyamine to medicinal compns. containing a pharmacol. active substance and a drug sorbefacient, therefore, the dose of the drug sorbefacient can be decreased and thus injuries on intestinal mucosa can be lessened or

prevented. Powder composition containing polyvinyl alc. 3.3, mannitol 10, sodium

lauryl sulfate 3, cilostazol 20, and taurine 3 g was prepared

IT 77883-43-3, Cardenalin 106463-17-6, Harnal

147816-23-7, Cefcapene pivoxil hydrochloride

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(medicinal compns. containing drugs, drug

absorption enhancers, and taurine compds. or polyamines)

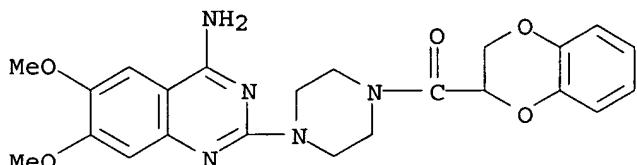
RN 77883-43-3 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8

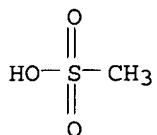
CMF C23 H25 N5 O5



CM 2

CRN 75-75-2

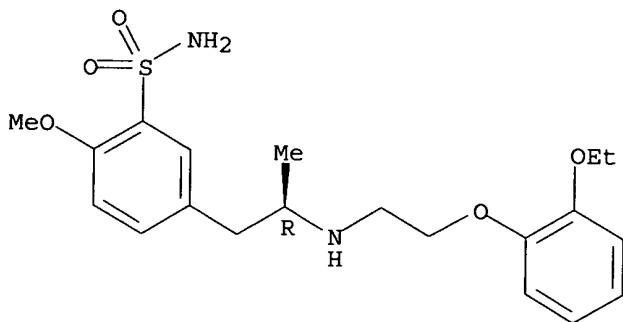
CMF C H4 O3 S



RN 106463-17-6 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

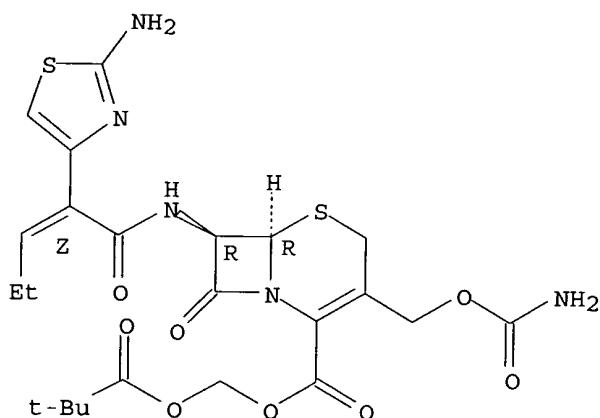


● HCl

RN 147816-23-7 HCPLUS

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 3-[(aminocarbonyl)oxy]methyl]-7-[[((2Z)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl)amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester,
 monohydrochloride, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



● HCl

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 18 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:754995 HCPLUS

DOCUMENT NUMBER: 137:268473

TITLE: Porous drug matrices and methods of manufacture thereof

INVENTOR(S): Straub, Julie; Altreuter, David; Bernstein, Howard;
 Chickering, Donald E.; Khattak, Sarwat; Randall, Greg

PATENT ASSIGNEE(S): Acusphere Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U. S.
6,395,300.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

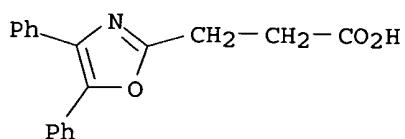
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002142050	A1	20021003	US 2002-53929	20020122 <--
US 6395300	B1	20020528	US 1999-433486	19991104 <--
EP 1642572	A1	20060405	EP 2005-27194	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 6645528	B1	20031111	US 2000-694407	20001023
US 6932983	B1	20050823	US 2000-706045	20001103
ZA 2001010347	A	20030730	ZA 2001-10347	20011218 <--
US 2005048116	A1	20050303	US 2004-924642	20040824
US 2005058710	A1	20050317	US 2004-928886	20040827
PRIORITY APPLN. INFO.:			US 1999-136323P	P 19990527
			US 1999-158659P	P 19991008
			US 1999-433486	A2 19991104
			US 2000-186310P	P 20000302
			EP 2000-939365	A3 20000525
			US 2002-53929	A3 20020122

AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a process that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solution and hydrophilic or hydrophobic excipients that stabilize the drug and inhibit crystallization, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. Hydrophobic or hydrophilic excipients may be selected to stabilize the drug in crystalline form by inhibiting crystal growth or to stabilize the drug in amorphous form by preventing crystallization. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Thus, 5.46 g of PEG 8000, 0.545 g of prednisone, and 0.055 g of Span 40 were dissolved in 182 mL of methylene chloride. A solution of 3.27 g of ammonium bicarbonate in 18.2 mL of water was added to the organic solution (phase ratio 1:10) and homogenized for 5 min at 16,000 RPM. The resulting emulsion was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas.

IT 21256-18-8, Oxaprozin 77883-43-3, Doxazosin mesylate 106463-17-6, Tamsulosin hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(porous drug matrixes and methods of manufacture thereof)

RN 21256-18-8 HCAPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



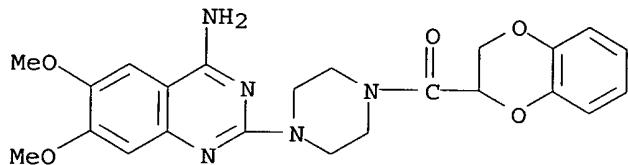
RN 77883-43-3 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8

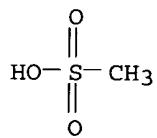
CMF C23 H25 N5 O5



CM 2

CRN 75-75-2

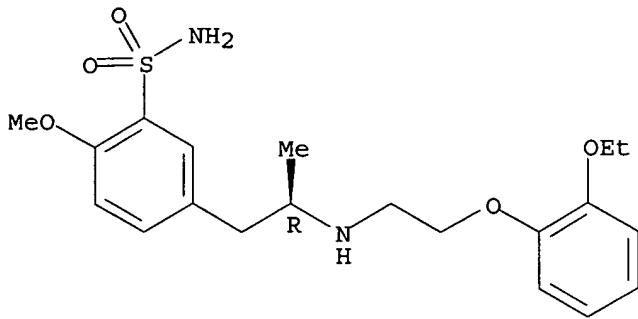
CMF C H4 O3 S



RN 106463-17-6 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L61 ANSWER 19 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:604460 HCPLUS

DOCUMENT NUMBER: 137:295216

TITLE: Selective Agonists at Group II Metabotropic Glutamate Receptors: Synthesis, Stereochemistry, and Molecular Pharmacology of (S)- and (R)-2-Amino-4-(4-hydroxy[1,2,5]thiadiazol-3-yl)butyric Acid

AUTHOR(S): Clausen, Rasmus P.; Braeuner-Osborne, Hans; Greenwood, Jeremy R.; Hermit, Mette B.; Stensbol, Tine B.; Nielsen, Birgitte; Krosgaard-Larsen, Povl

CORPORATE SOURCE: Neuroscience PharmaBiotec Research Center Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Copenhagen, DK-2100, Den.

SOURCE: Journal of Medicinal Chemistry (2002), 45(19), 4240-4245

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:295216

AB Homologation of analogs of the central excitatory neurotransmitter glutamic acid (Glu), in which the distal carboxy group has been bioisostERICALLY replaced by acidic heterocyclic units, has previously provided subtype selective ligands for metabotropic Glu receptors (mGluRs). For example, the Glu analog, (S)-2-amino-3-(4-hydroxy[1,2,5]thiadiazol-3-yl)propionic acid (TDPA), is an 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) receptor agonist, which in addition stereospecifically activates group I mGluRs. The authors have synthesized the TDPA homologs, (S)- and (R)-2-amino-4-(4-hydroxy[1,2,5]thiadiazol-3-yl)butyric acid (I) and shown that whereas neither enantiomer interacts with AMPA receptors, both isomers appear to be selective and equipotent agonists at group II mGluRs as represented by the mGluR2 subtype. The activities of (S)-I and (R)-I are rationalized by conformational anal., by comparison with the potent and specific group II mGluR agonist LY379268, and by docking to a homol. model of mGluR2.

IT 467428-40-6P 467428-41-7P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);

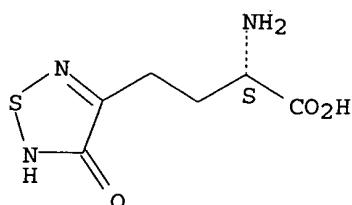
BIOL (Biological study); PREP (Preparation)

(preparation and agonist activity of amino(hydroxythiadiazolyl)butyric acid at group II metabotropic glutamate receptors)

RN 467428-40-6 HCPLUS

CN 1,2,5-Thiadiazole-3-butanoic acid, α -amino-4,5-dihydro-4-oxo-,
(α S)- (9CI) (CA INDEX NAME)

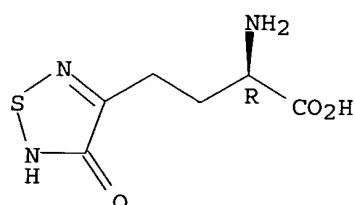
Absolute stereochemistry. Rotation (+).



RN 467428-41-7 HCPLUS

CN 1,2,5-Thiadiazole-3-butanoic acid, α -amino-4,5-dihydro-4-oxo-,
(α R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



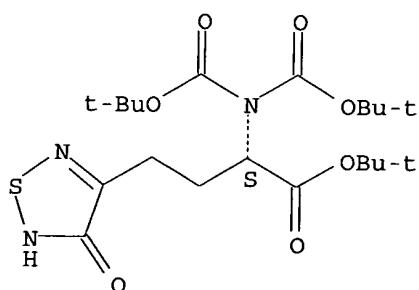
IT 467428-39-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)(preparation and agonist activity of amino(hydroxythiadiazolyl)butyric acid
at group II metabotropic glutamate receptors)

RN 467428-39-3 HCPLUS

CN 1,2,5-Thiadiazole-3-butanoic acid, α -[bis[(1,1-dimethylethoxy)carbonyl]amino]-4,5-dihydro-4-oxo-, 1,1-dimethylethyl
ester, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

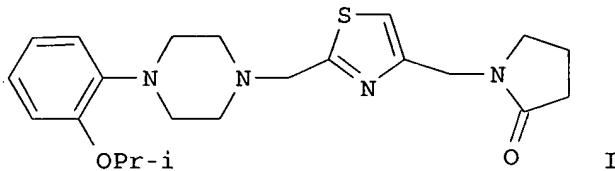


REFERENCE COUNT:

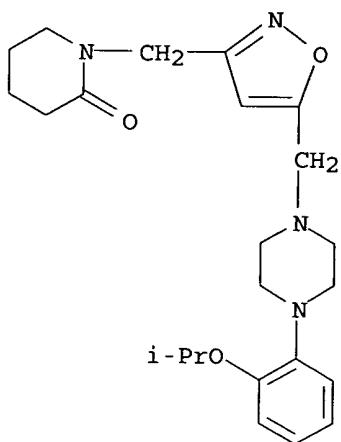
39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 20 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:585086 HCPLUS
 DOCUMENT NUMBER: 138:89769
 TITLE: Arylpiperazine substituted heterocycles as Selective
 α 1a adrenergic antagonists
 AUTHOR(S): Khatuya, Haripada; Hutchings, Richard H.; Kuo,
 Gee-Hong; Pulito, Virginia L.; Jolliffe, Linda K.; Li,
 Xiaobing; Murray, William V.
 CORPORATE SOURCE: Drug Discovery Research, Johnson & Johnson
 Pharmaceutical Research and Development LLC, Raritan,
 NJ, 08869, USA
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2002
), 12(17), 2443-2446
 CODEN: BMCL8; ISSN: 0960-894X
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 138:89769
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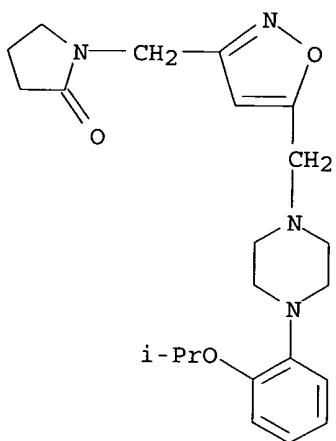


- AB Antagonists of the α 1-adrenergic receptors (α 1-ARs) are useful for the treatment of benign prostatic hyperplasia. A series of potent and subtype-selective α 1a-AR antagonists has been synthesized, e.g. I, displaying in vitro binding affinity in the low the nanomolar range.
- IT 171855-22-4P 223253-19-8P 223253-90-5P
 483987-65-1P 483987-68-4P 483987-71-9P
 483987-72-0P 483987-73-1P 483987-74-2P
 483987-75-3P 483987-76-4P 483987-77-5P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of arylpiperazine substituted heterocycles as selective α 1a adrenergic antagonists)
- RN 171855-22-4 HCPLUS
- CN 2-Piperidinone, 1-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)



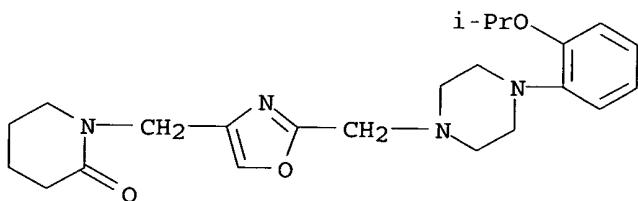
RN 223253-19-8 HCPLUS

CN 2-Pyrrolidinone, 1-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)



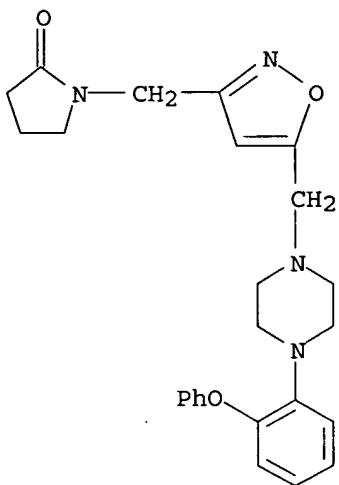
RN 223253-90-5 HCPLUS

CN 2-Piperidinone, 1-[[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)

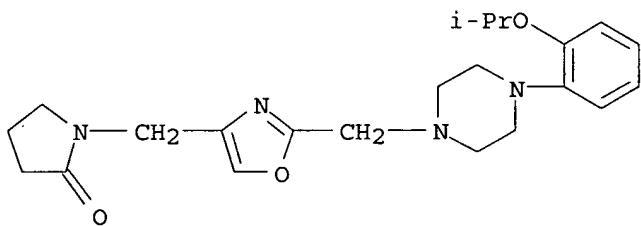


RN 483987-65-1 HCPLUS

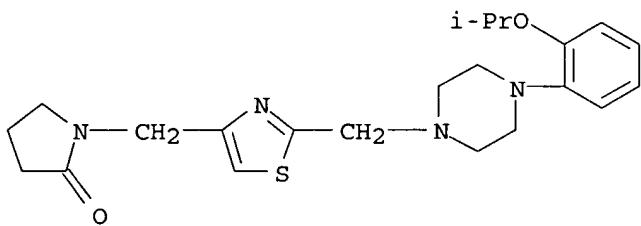
CN 2-Pyrrolidinone, 1-[[5-[[4-(2-phenoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)



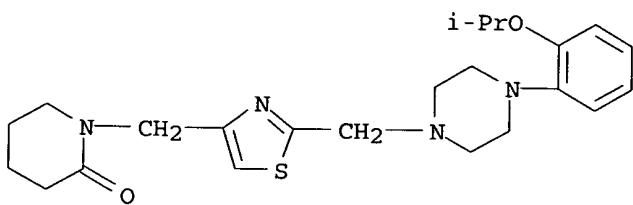
RN 483987-68-4 HCAPLUS
CN 2-Pyrrolidinone, 1-[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-oxazolyl]methyl] - (9CI) (CA INDEX NAME)



RN 483987-71-9 HCAPLUS
CN 2-Pyrrolidinone, 1-[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-thiazolyl]methyl] - (9CI) (CA INDEX NAME)

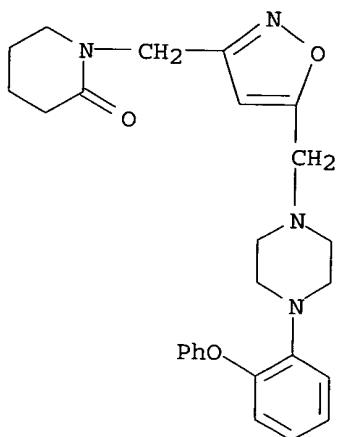


RN 483987-72-0 HCAPLUS
CN 2-Piperidinone, 1-[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-thiazolyl]methyl] - (9CI) (CA INDEX NAME)



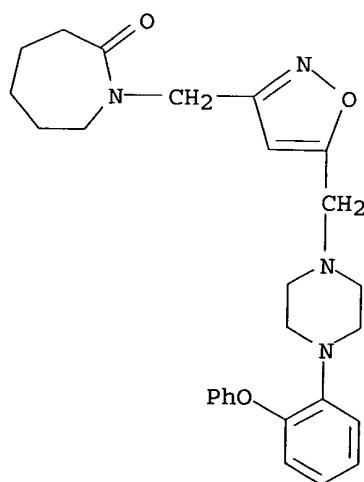
RN 483987-73-1 HCAPLUS

CN 2-Piperidinone, 1-[[5-[[4-(2-phenoxyphenyl)-1-piperazinyl]methyl]-3-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)



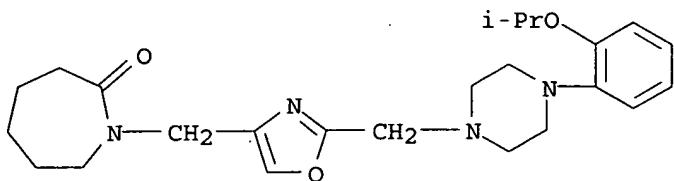
RN 483987-74-2 HCAPLUS

CN 2H-Azepin-2-one, hexahydro-1-[[5-[[4-(2-phenoxyphenyl)-1-piperazinyl]methyl]-3-isoxazolyl]methyl]- (9CI) (CA INDEX NAME)



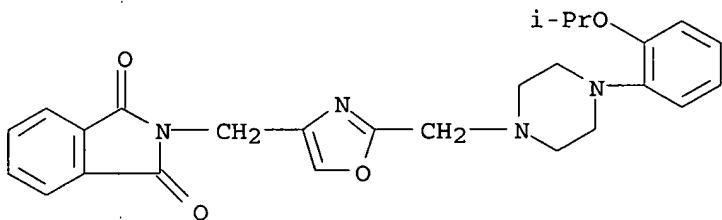
RN 483987-75-3 HCAPLUS

CN 2H-Azepin-2-one, hexahydro-1-[[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-oxazolyl]methyl]- (9CI) (CA INDEX NAME)



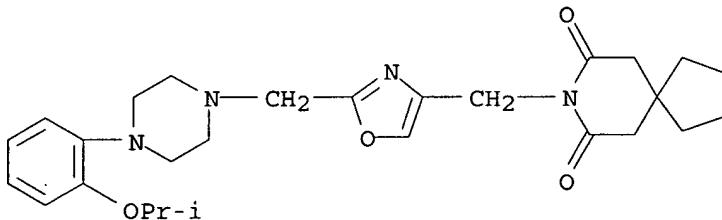
RN 483987-76-4 HCPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-[[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-oxazolyl]methyl] - (9CI) (CA INDEX NAME)



RN 483987-77-5 HCPLUS

CN 8-Azaspiro[4.5]decane-7,9-dione, 8-[[2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-4-oxazolyl]methyl] - (9CI) (CA INDEX NAME)



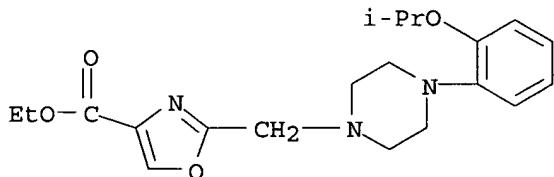
IT 483987-66-2P 483987-67-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

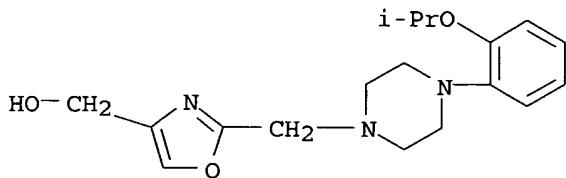
(preparation of arylpiperazine substituted heterocycles as selective
α_{1A} adrenergic antagonists)

RN 483987-66-2 HCPLUS

CN 4-Oxazolecarboxylic acid, 2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 483987-67-3 HCAPLUS
 CN 4-Oxazolemethanol, 2-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl] -
 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

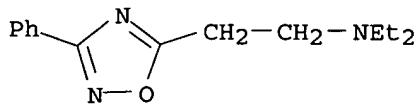
L61 ANSWER 21 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:573318 HCAPLUS
 DOCUMENT NUMBER: 137:129885
 TITLE: Aqueous pharmaceutical solutions with trisubstituted glycyrrhizic acid salts
 INVENTOR(S): Baiocchi, Leandro; De Gregorio, Mauro
 PATENT ASSIGNEE(S): Italy
 SOURCE: Eur. Pat. Appl., 15 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1226831	A1	20020731	EP 2002-75334	20020128 <-
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2002284673	A2	20021002	JP 2002-19490	20020129 <-
US 2002193322	A1	20021219	US 2002-58080	20020129 <-
US 6699841	B2	20040302		

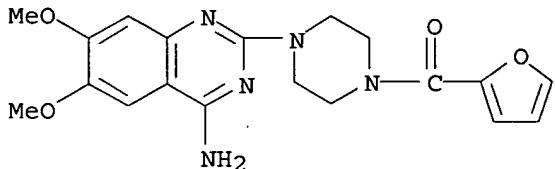
PRIORITY APPLN. INFO.: IT 2001-RM48 A 20010130
 AB A method of forming an aqueous solution containing (i) a first physiol. acceptable

compound of an acidic nature and a second physiol. acceptable compound of a basic nature which give rise to mutual precipitate in water, and (ii) a trisubstituted salt of glycyrrhizic acid in a sufficient quantity to form a clear solution in water. For example, a solution of diclofenac, tetryzoline, and benzalkonium chloride was prepared containing diclofenac sodium 100 mg, tetryzoline hydrochloride 50 mg, benzalkonium chloride 10 mg, a solution containing 8.34% disodium monoammonium glycyrrhizinate 1.2 g, and water up to 100 mL.

IT 959-14-8, Oxolamine 19216-56-9, Prazosin
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (aqueous solns. of acidic and basic drugs containing trisubstituted glycyrrhizic acid salts as solubilizers)
 RN 959-14-8 HCAPLUS
 CN 1,2,4-Oxadiazole-5-ethanamine, N,N-diethyl-3-phenyl- (9CI) (CA INDEX NAME)



RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 22 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:555334 HCAPLUS
 DOCUMENT NUMBER: 137:114525
 TITLE: Syntactic deformable pharmaceutical foam compositions
 INVENTOR(S): Odidi, Isa; Odidi, Amina
 PATENT ASSIGNEE(S): Can.
 SOURCE: PCT Int. Appl., 47 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002056861	A2	20020725	WO 2002-CA54	20020117 <--
WO 2002056861	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6800668	B1	20041005	US 2001-765783	20010119
CA 2435276	AA	20020725	CA 2002-2435276	20020117 <--
CA 2435276	C	20050315		
AU 2002226223	A1	20020730	AU 2002-226223	20020117 <--
PRIORITY APPLN. INFO.:			US 2001-765783	A 20010119
			WO 2002-CA54	W 20020117

AB The invention relates to methods for preparing a syntactic foam composition suitable for use as a carrier for chems. or other compds., including pharmaceuticals. Carbopol 971P, hydroxyethyl cellulose, cellulose microspheres and silica, was mixed in a high-shear mixer. The resulting admixt. was treated with 2-propanol, while simultaneously subjecting the

admixt. to high-shear forces in the high-shear mixer. This mixing created a uniform stable syntactic deformable and compressible dendritic solid foam which could be shaped before drying. Metoprolol succinate was added to the above admixt. and subjected to high-shear agitation for 2 min before treatment with 2-propanol. A stable syntactic deformable and compressible dendritic solid foam which could be shaped before drying was obtained. This was dried at 40°. The dried foam was then disentangled by size reduction to obtain discrete particles. The free flowing particles were reassembled and shaped by compression in a mold. The shaped units, when subjected to an aqueous medium, released metoprolol over a period of <3 h.

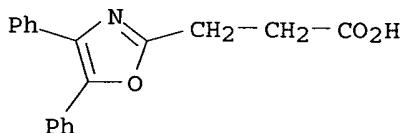
IT 21256-18-8, Oxaprozin 63590-64-7, Terazosin
74191-85-8, Doxazosin 106133-20-4,

Tamsulosin 124937-51-5, Tolterodine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(syntactic deformable pharmaceutical foam compns.)

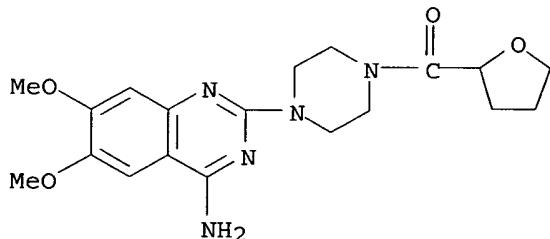
RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



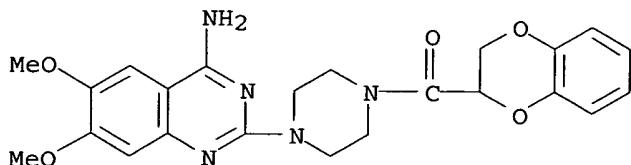
RN 63590-64-7 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCPLUS

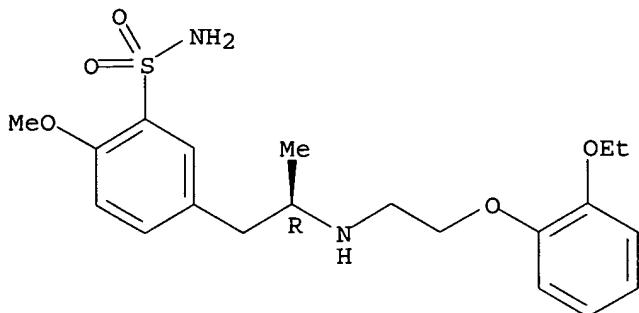
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

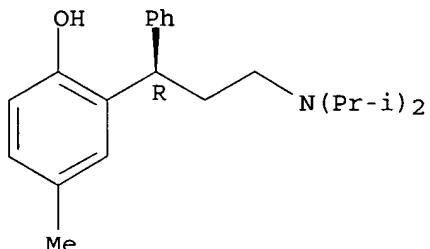
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L61 ANSWER 23 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:531823 HCPLUS

DOCUMENT NUMBER: 137:232888

TITLE: (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-methylcyclopropyl)Glycine Is a Potent and Selective Metabotropic Group 2 Receptor Agonist with Anxiolytic Properties

AUTHOR(S): Collado, Ivan; Pedregal, Concepcion; Mazon, Angel; Felix Espinosa, Juan; Blanco-Urgoiti, Jaime; Schoepp, Darryle D.; Wright, Rebecca A.; Johnson, Bryan G.; Kingston, Ann E.

CORPORATE SOURCE: Lilly SA, Madrid, 28108, Spain

SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3619-3629

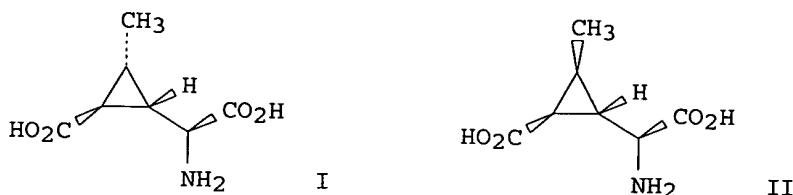
PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623 American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:232888

GI



AB The asym. synthesis and biol. activity of (2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-methylcyclopropyl)glycine I and its epimer II (at the C3' center) are described. I is a highly potent and selective agonist for group 2 metabotropic glutamate receptors (mGluRs). It is also systemically 4 orders of magnitude more active in the fear-potentiated startle model of anxiety in rats than the rigid constrained bicyclic system LY354740. In summary, the authors have shown that high mol. complexity of conformationally constrained bicyclic systems is not a requirement to achieve highly selective and potent group 2 mGluRs agonists.

IT 457939-76-3P 457939-78-5P 457939-79-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

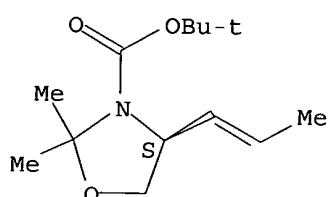
(asym. preparation of [(carboxy)(methyl)cyclopropyl]glycine and its biol. activity as a potent and selective metabotropic glutamate receptor agonist with anxiolytic properties)

RN 457939-76-3 HCPLUS

CN 3-Oxazolidinecarboxylic acid, 2,2-dimethyl-4-(1-propenyl)-, 1,1-dimethylethyl ester, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

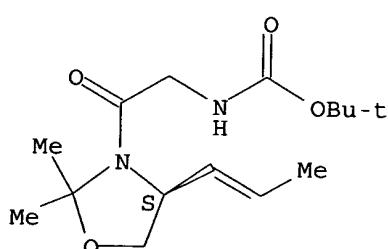


RN 457939-78-5 HCPLUS

CN Carbamic acid, [2-[(4S)-2,2-dimethyl-4-(1-propenyl)-3-oxazolidinyl]-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

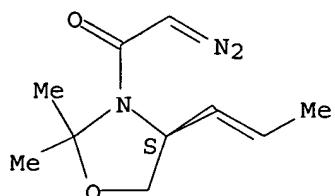
Absolute stereochemistry.

Double bond geometry unknown.



RN 457939-79-6 HCAPLUS
 CN Oxazolidine, 3-(diazoacetyl)-2,2-dimethyl-4-(1-propenyl)-, (4S)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry unknown.

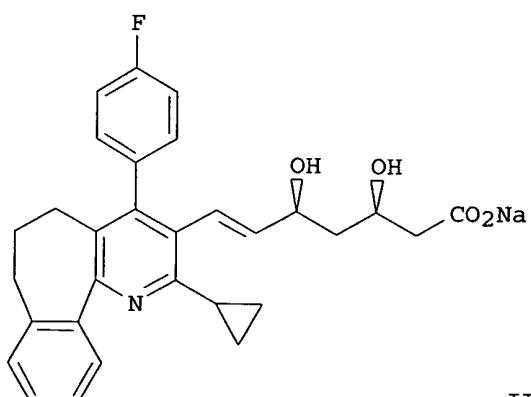
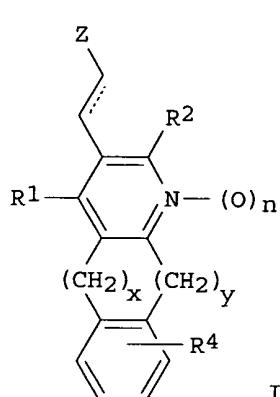


REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 24 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:392237 HCAPLUS
 DOCUMENT NUMBER: 136:401651
 TITLE: Preparation of fused pyridine derivatives as HMG-CoA reductase inhibitors
 INVENTOR(S): Robl, Jeffrey A.; Chen, Bang-Chi; Sun, Chong-Qing
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 875,218.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002061901	A1	20020523	US 2001-8154	20011204 <--
US 6620821	B2	20030916		
US 2002028826	A1	20020307	US 2001-875218	20010606 <--
US 2004024216	A1	20040205	US 2003-602753	20030624
PRIORITY APPLN. INFO.:			US 2000-211594P	P 20000615
			US 2001-875218	A2 20010606
			US 2001-8154	A3 20011204

OTHER SOURCE(S): MARPAT 136:401651
 GI



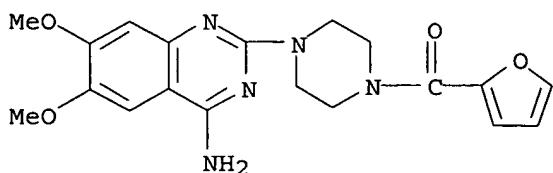
AB The title compds. I and their pharmaceutically acceptable salts, esters, prodrug esters, and stereoisomers are claimed [wherein: Z = CH(OH)CH₂CR₇(OH)CH₂CO₂R₃ or corresponding pyranone lactone derivs.; n = 0, 1; x = 0, 1, 2, 3, or 4; y = 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0; and optionally one or more carbons of (CH₂)_x and/or (CH₂)_y together with addnl. carbons form a 3 to 7 membered spirocyclic ring; R₁, R₂ = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R₃ = H or lower alkyl; R₄ = H, halo, CF₃, OH, alkyl, alkoxy, CO₂H, (un)substituted NH₂, cyano, (un)substituted CONH₂, etc.; R₇ = H, alkyl]. The compds. are HMG-CoA reductase inhibitors, and are active in inhibiting cholesterol biosynthesis and modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol (no data). I are thus useful in treating hyperlipidemia and dyslipidemia, in hormone replacement therapy, and in treating hypercholesterolemia, hypertriglyceridemia and atherosclerosis, as well as Alzheimer's disease and osteoporosis. Preps. of several compds. are described. For instance, a multistep synthesis of fused pyridine derivative II is reported. Compds. I may be used in a manner similar to atorvastatin, pravastatin, simvastatin, etc. Combinations of compds. I with various other drugs are claimed, the latter being specified as certain pharmacol. classes, as inhibitors of specific enzymes, as (ant)agonists of specific receptors, and as numerous named drugs.

IT 19237-84-4, Prazosin hydrochloride 170861-63-9
, JTT-501 196808-45-4 335149-19-4, GW-409544

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. also containing; preparation of fused pyridine derivs. as HMG-CoA reductase inhibitors)

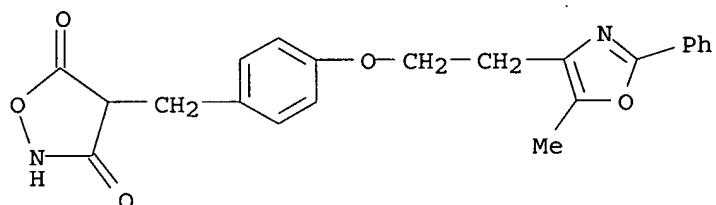
RN 19237-84-4 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride (9CI) (CA INDEX NAME)



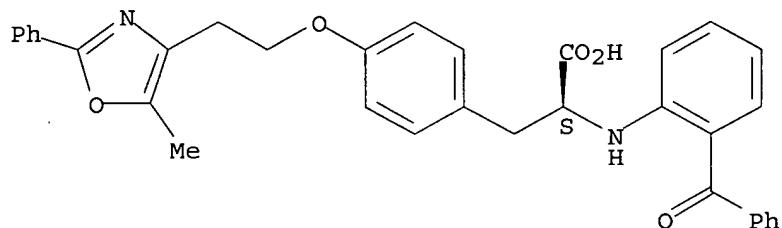
● HCl

RN 170861-63-9 HCAPLUS
 CN 3,5-Isoxazolidinedione, 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl - (9CI) (CA INDEX NAME)



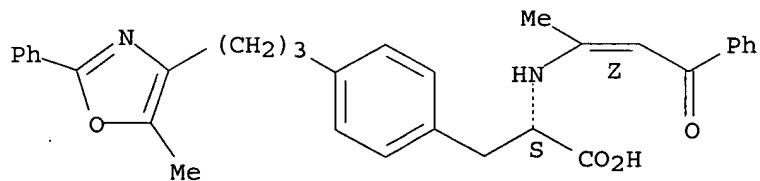
RN 196808-45-4 HCAPLUS
 CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 335149-19-4 HCAPLUS
 CN L-Phenylalanine, N-[(1Z)-1-methyl-3-oxo-3-phenyl-1-propenyl]-4-[3-(5-methyl-2-phenyl-4-oxazolyl)propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

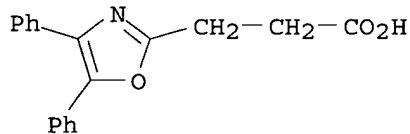


L61 ANSWER 25 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:392219 HCAPLUS
 DOCUMENT NUMBER: 136:406945
 TITLE: Methods for in vivo drug delivery based on monitoring blood flow parameters
 INVENTOR(S): Kensey, Kenneth R.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 727,950.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

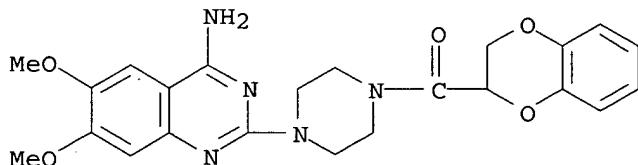
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002061835	A1	20020523	US 2001-828761	20010409 <--
US 6019735	A	20000201	US 1997-919906	19970828 <--
CA 2301161	AA	19990304	CA 1998-2301161	19980826 <--
NZ 502905	A	20010831	NZ 1998-502905	19980826 <--
JP 2001514384	T2	20010911	JP 2000-507994	19980826 <--
US 6322524	B1	20011127	US 1999-439795	19991112 <--
US 6322525	B1	20011127	US 2000-501856	20000210 <--
NO 2000000944	A	20000225	NO 2000-944	20000225 <--
US 6428488	B1	20020806	US 2000-615340	20000712 <--
WO 2002043806	A2	20020606	WO 2001-US44352	20011127 <--
WO 2002043806	A3	20030327		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002026986	A5	20020611	AU 2002-26986	20011127 <--
US 2002088953	A1	20020711	US 2001-33841	20011227 <--
US 6624435	B2	20030923		
WO 2002079778	A2	20021010	WO 2002-US3984	20020207 <--
WO 2002079778	A3	20030710		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002184941	A1	20021212	US 2002-156165	20020528 <--
US 6571608	B2	20030603		
PRIORITY APPLN. INFO.: US 1997-919906 A2 19970828				
US 1999-439795 A2 19991112				
US 2000-501856 A2 20000210				

US	2000-628401	A2	20000801
US	2000-727950	A2	20001201
US	1997-966076	A	19971107
WO	1998-US17657	W	19980826
US	2000-615340	A3	20000712
US	2000-228612P	P	20000828
US	2001-789350	B2	20010221
US	2001-819924	A	20010328
US	2001-828761	A	20010409
US	2001-839785	A	20010420
US	2001-841389	A	20010424
US	2001-897164	A3	20010702
WO	2001-US44352	W	20011127

- AB Various methods are provided for determining and utilizing the viscosity of the circulating blood of a living being over a range of shear rates for diagnostics and treatment, such as detecting/reducing blood viscosity, work of the heart, contractility of the heart, for detecting/reducing the surface tension of the blood, for detecting plasma viscosity, for explaining/countering endothelial cell dysfunction, for providing high and low blood vessel wall shear stress data, red blood cell deformability data, lubricity of blood, and for treating different ailments such as peripheral arterial disease in combination with administering to a living being at least one pharmaceutically acceptable agent. Agents pharmaceutically effective to regulate at least one of the aforementioned blood parameters are used to adjust distribution of a substance through the bloodstream.
- IT 21256-18-8, Oxaprozin 74191-85-8, Doxazosin
124937-51-5, Tolterodine 173324-94-2,
Temiverine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for in vivo drug delivery based on monitoring blood flow parameters)
- RN 21256-18-8 HCPLUS
CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)

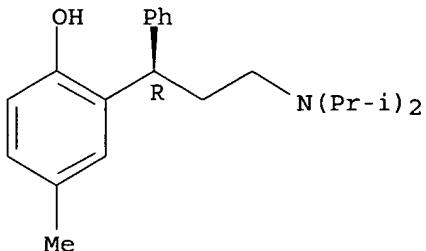


- RN 74191-85-8 HCPLUS
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



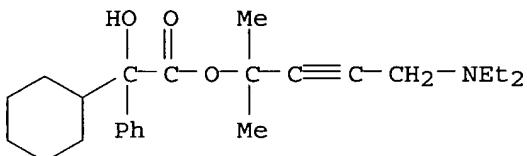
- RN 124937-51-5 HCPLUS
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173324-94-2 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
4-(diethylamino)-1,1-dimethyl-2-butynyl ester (9CI) (CA INDEX NAME)



L61 ANSWER 26 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:354556 HCPLUS

DOCUMENT NUMBER: 137:98838

TITLE: Molecular Properties That Influence the Oral Bioavailability of Drug Candidates

AUTHOR(S): Weber, Daniel F.; Johnson, Stephen R.; Cheng, Hung-Yuan; Smith, Brian R.; Ward, Keith W.; Kopple, Kenneth D.

CORPORATE SOURCE: Departments of Medicinal Chemistry, Cheminformatics, Computational Analytical and Structural Sciences, and Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, King of Prussia, PA, 19406-0939, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(12), 2615-2623

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

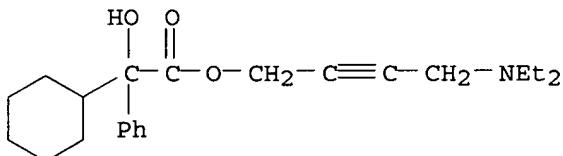
LANGUAGE: English

AB Oral bioavailability measurements in rats for over 1100 drug candidates studied at Smith-Kline Beecham Pharmaceuticals (now Glaxo Smith-Kline) have allowed us to analyze the relative importance of mol. properties considered to influence that drug property. Reduced mol. flexibility, as measured by the number of rotatable bonds, and low polar surface area or total hydrogen bond count (sum of donors and acceptors) are found to be important predictors of good oral bioavailability, independent of mol. weight. That on average both the number of rotatable bonds and polar surface area or hydrogen bond count tend to increase with mol. weight may in part explain the success of the mol. weight parameter in predicting oral bioavailability. The commonly applied mol. weight cutoff at 500 does not itself significantly sep. compds. with poor oral bioavailability from those with acceptable values in this extensive data set. Our observations suggest that compds. which meet only the 2 criteria of (1) 10 or fewer rotatable bonds and (2) polar surface area \leq 140 Å² (or 12 or fewer H-bond donors and

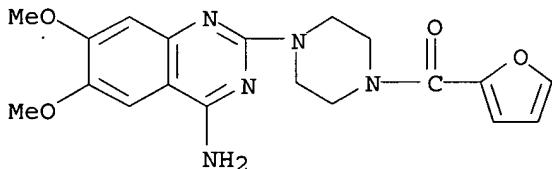
acceptors) will have a high probability of good oral bioavailability in the rat. Data sets for the artificial membrane permeation rate and for clearance in the rat were also examined. Reduced polar surface area correlates better with increased permeation rate than does lipophilicity ($C \log P$), and increased rotatable bond count has a neg. effect on the permeation rate. A threshold permeation rate is a prerequisite of oral bioavailability. The rotatable bond count does not correlate with the data examined here for the in vivo clearance rate in the rat.

IT 5633-20-5, Oxybutynin 19216-56-9,
 Prazosin 63590-64-7, Terazosin
 106133-20-4, Tamsulosin 124937-51-5,
 Tolterodine 139264-17-8, Zolmitriptan
 RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (mol. properties effect on oral bioavailability of drug
 candidates)

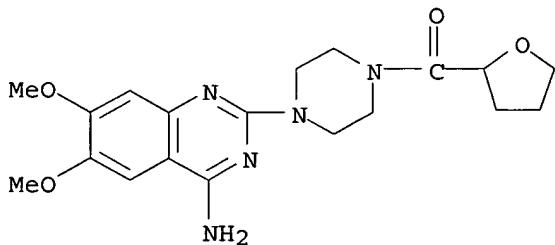
RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butylyn ester (9CI) (CA INDEX NAME)



RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-
 (9CI) (CA INDEX NAME)



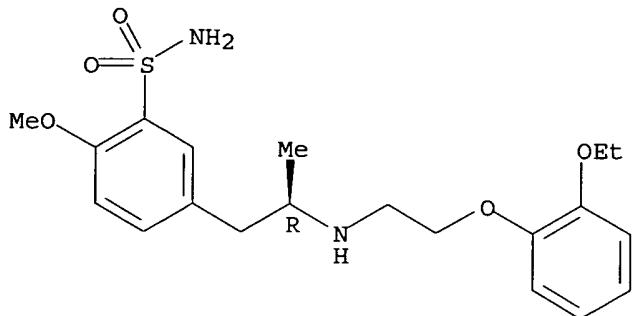
RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS
 CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-

methoxy- (9CI) (CA INDEX NAME)

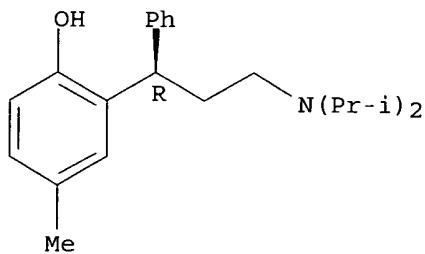
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCAPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

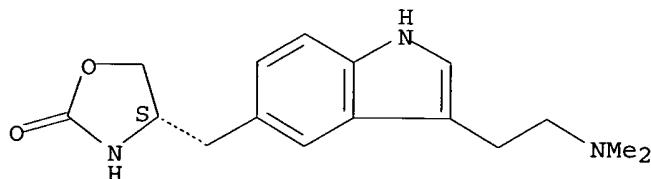
Absolute stereochemistry. Rotation (+).



RN 139264-17-8 HCAPLUS

CN 2-Oxazolidinone, 4-[[3-[(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

35

THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 27 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:324938 HCAPLUS

DOCUMENT NUMBER: 137:304641

TITLE: 2-Amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid: resolution, absolute stereochemistry and enantiopharmacology at glutamate receptors

AUTHOR(S): Johansen, Tommy N.; Janin, Yves L.; Nielsen, Birgitte; Frydenvang, Karla; Brauner-Osborne, Hans; Stensbol,

Tine B.; Vogensen, Stine B.; Madsen, Ulf;
Krogsgaard-Larsen, Povl

CORPORATE SOURCE: Department of Medicinal Chemistry, NeuroScience
PharmaBiotec Research Center, The Royal Danish School
of Pharmacy, Copenhagen, DK-2100, Den.

SOURCE: Bioorganic & Medicinal Chemistry (2002),
10(7), 2259-2266

CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In order to identify new subtype-selective (S)-glutamate (Glu) receptor ligands we have synthesized (RS)-2-amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid [(RS)-TDPA]. Resolution of (RS)-TDPA by chiral chromatog. was performed using a Crownpac CR(+) column affording (R)- and (S)-TDPA of high enantiomeric purity (enantiomeric excess=99.9%). An x-ray crystallog. anal. revealed that the early eluting enantiomer has R-configuration. Both enantiomers showed high affinity as well as high agonist activity at (RS)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptors, determined using a [3H]AMPA binding assay and an electrophysiolog. model, resp. The affinities and agonist activities obtained for (R)-TDPA ($IC_{50}=0.265 \mu M$ and $EC_{50}=6.6 \mu M$, resp.) and (S)-TDPA ($IC_{50}=0.065 \mu M$ and $EC_{50}=20 \mu M$, resp.) revealed a remarkably low AMPA receptor stereoselectivity, (S)-TDPA showing the highest affinity and (R)-TDPA the most potent agonist activity. In addition, (S)-TDPA was shown to interact with synaptosomal Glu uptake sites displacing [3H] (R)-aspartic acid ($IC_{50} \approx 390 \mu M$). An enantiospecific and subtype-selective agonist activity was observed for (S)-TDPA at group I metabotropic Glu (mGlu) receptors ($EC_{50}=13 \mu M$ at mGlu5 and $EC_{50}=95 \mu M$ at mGlu1).

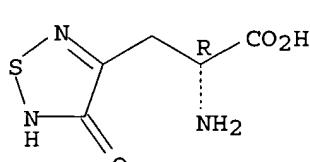
IT 313352-02-2P 313352-03-3P 472965-79-0P

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(2-amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid enantiomers resolution, absolute stereochem. and enantiopharmacol. at glutamate receptors)

RN 313352-02-2 HCPLUS

CN 1,2,5-Thiadiazole-3-propanoic acid, α -amino-4,5-dihydro-4-oxo-,
(α R)- (9CI) (CA INDEX NAME)

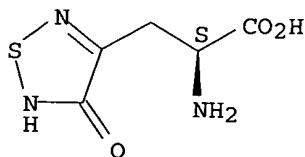
Absolute stereochemistry. Rotation (-).



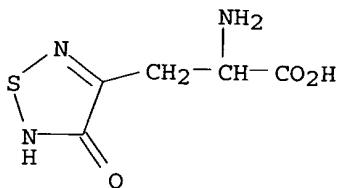
RN 313352-03-3 HCPLUS

CN 1,2,5-Thiadiazole-3-propanoic acid, α -amino-4,5-dihydro-4-oxo-,
(α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 472965-79-0 HCAPLUS

CN 1,2,5-Thiadiazole-3-propanoic acid, α -amino-4,5-dihydro-4-oxo- (9CI)
(CA INDEX NAME)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 28 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:227327 HCAPLUS

DOCUMENT NUMBER: 137:148

TITLE: A Computational Ensemble Pharmacophore Model for Identifying Substrates of P-Glycoprotein

AUTHOR(S): Penzotti, Julie E.; Lamb, Michelle L.; Evensen, Erik; Grootenhuis, Peter D. J.

CORPORATE SOURCE: Deltagen Research Laboratories, San Diego, CA, 92121, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(9), 1737-1740

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

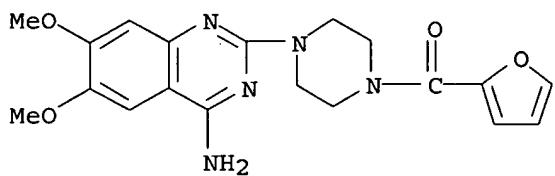
AB P-glycoprotein (P-gp) functions as a drug efflux pump, mediating multidrug resistance and limiting the efficacy of many drugs. Clearly, identification of potential P-gp substrate liability early in the drug discovery process would be advantageous. We describe a multiple-pharmacophore model that can discriminate between substrates and nonsubstrates of P-gp with an accuracy of 63%. The application of this filter allows large virtual libraries to be screened efficiently for compds. less likely to be transported by P-gp.

IT 19216-56-9, PRAZOSIN 152044-53-6, EPOTHILONE A
RL: PRP (Properties)

(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)

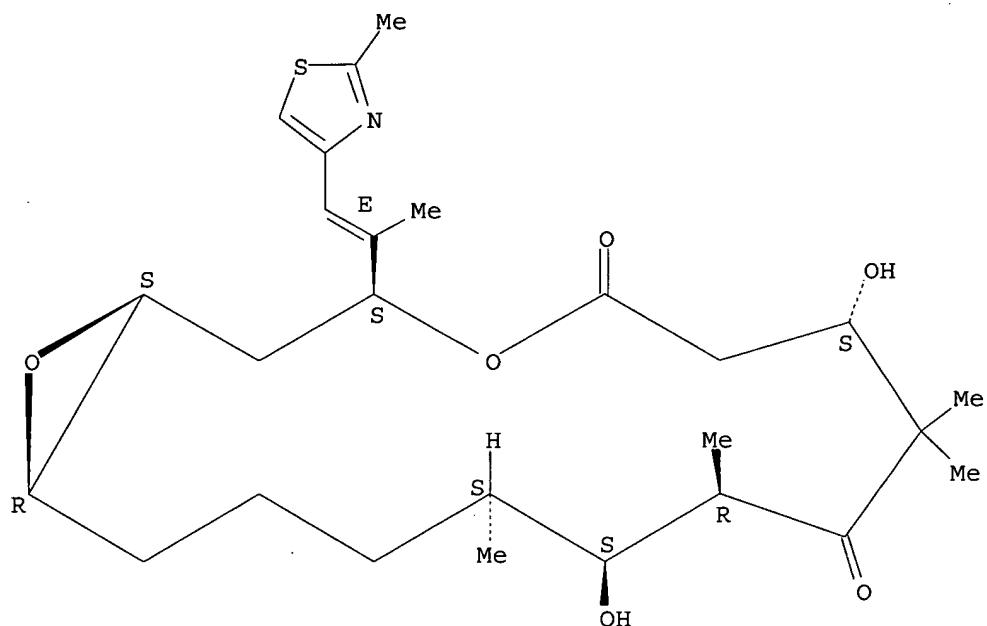


RN 152044-53-6 HCAPLUS

CN 4,17-Dioxabicyclo[4.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



REFERENCE COUNT:

56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 29 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:185688 HCAPLUS

DOCUMENT NUMBER: 136:252567

TITLE: Methods for drug administration and distribution based on monitoring blood viscosity and other parameters for diagnostics and treatment

INVENTOR(S): Kensey, Kenneth

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 819,924.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002032149	A1	20020314	US 2001-841389	20010424 <--
US 6019735	A	20000201	US 1997-919906	19970828 <--
CA 2301161	AA	19990304	CA 1998-2301161	19980826 <--
NZ 502905	A	20010831	NZ 1998-502905	19980826 <--
JP 2001514384	T2	20010911	JP 2000-507994	19980826 <--
US 6322524	B1	20011127	US 1999-439795	19991112 <--
US 6322525	B1	20011127	US 2000-501856	20000210 <--
NO 2000000944	A	20000225	NO 2000-944	20000225 <--
US 6428488	B1	20020806	US 2000-615340	20000712 <--
US 2002088953	A1	20020711	US 2001-33841	20011227 <--
US 6624435	B2	20030923		
WO 2002079778	A2	20021010	WO 2002-US3984	20020207 <--
WO 2002079778	A3	20030710		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002184941	A1	20021212	US 2002-156165	20020528 <--
US 6571608	B2	20030603		

PRIORITY APPLN. INFO.:

US 1997-919906	A2 19970828
US 1999-439795	A2 19991112
US 2000-501856	A2 20000210
US 2000-628401	A2 20000801
US 2000-727950	A2 20001201
US 2001-819924	A2 20010328
US 1997-966076	A 19971107
WO 1998-US17657	W 19980826
US 2000-615340	A3 20000712
US 2000-228612P	P 20000828
US 2001-789350	B2 20010221
US 2001-828761	A 20010409
US 2001-839785	A 20010420
US 2001-841389	A 20010424
US 2001-897164	A3 20010702

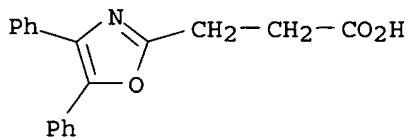
AB Various methods are provided for determining and utilizing the viscosity of the circulating blood of a living being, i.e., a human, over a range of shear rates for diagnostics and treatment, such as detecting/reducing blood viscosity, work of the heart, contractility of the heart, for detecting/reducing the surface tension of the blood, for detecting plasma viscosity, for explaining/countering endothelial cell dysfunction, for providing high and low blood vessel wall shear stress data, red blood cell deformability data, lubricity of blood, and for treating different ailments such as peripheral arterial disease in combination with administering to a living being at least one pharmaceutically acceptable agent. Agents pharmaceutically effective to regulate at least one of the aforementioned blood parameters are used to adjust distribution of a substance through the bloodstream. For example, when blood viscosity is a blood flow parameter monitored, an agent is selected from i.v. diluents, red blood cell deformability agents, antiurea agents, oral contraceptives, antidiabetic agents, antiarrhythmics, antihypertensives, antihyperlipidemics, antiplatelet agents, appetite suppressants, antiobesity agents, blood modifiers, smoking deterrent agents, and

nutritional supplements.

IT 21256-18-8, Oxaprozin 74191-85-8, Doxazosin
 124937-51-5, Tolterodine 173324-94-2,
 Temiverine
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (apparatus and methods for monitoring blood viscosity and other parameters
 in drug delivery for diagnostics and treatment)

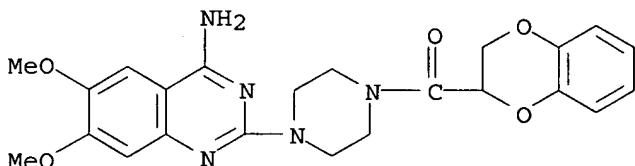
RN 21256-18-8 HCAPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS

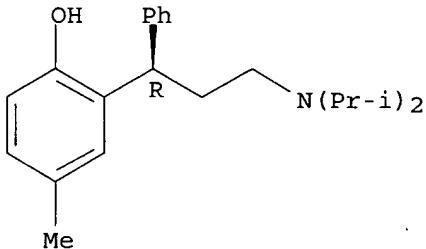
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 124937-51-5 HCAPLUS

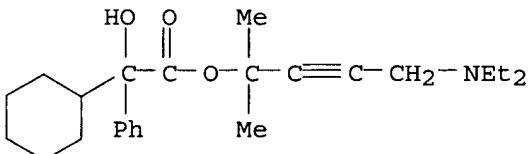
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173324-94-2 HCAPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester (9CI) (CA INDEX NAME)



L61 ANSWER 30 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:107160 HCPLUS
 DOCUMENT NUMBER: 136:161366
 TITLE: Epoxy-steroidal aldosterone antagonist and calcium channel blocker combination therapy for treatment of congestive heart failure and other cardiovascular disorders
 INVENTOR(S): Schuh, Joseph R.
 PATENT ASSIGNEE(S): Pharmacia Corporation, USA
 SOURCE: PCT Int. Appl., 231 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

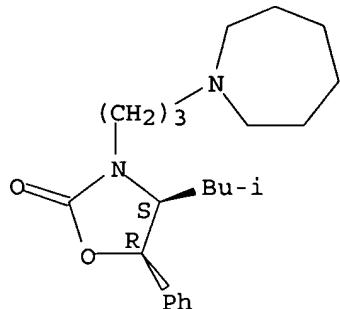
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009761	A2	20020207	WO 2001-US23677	20010727 <--
WO 2002009761	A3	20030103		
WO 2002009761	C2	20030710		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2415826	AA	20020207	CA 2001-2415826	20010727 <--
AU 2001078045	A5	20020213	AU 2001-78045	20010727 <--
EP 1303305	A2	20030423	EP 2001-956001	20010727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004505061	T2	20040219	JP 2002-515313	20010727
US 2003220310	A1	20031127	US 2003-343165	20030127
PRIORITY APPLN. INFO.:			US 2000-221359P	P 20000727
			WO 2001-US23677	W 20010727

- AB A combination therapy comprising a therapeutically effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically effective amount of a calcium channel blocker is described for treatment of circulatory disorders, including cardiovascular disorders such as hypertension, congestive heart failure, cirrhosis and ascites. Preferred calcium channel blockers are those compds. having high potency and bioavailability. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidals compds. characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. A preferred combination therapy includes the calcium channel blocker verapamil-HCl and the aldosterone receptor antagonist epoxymexrenone.
- IT 104454-71-9, Ipenoxazone 129927-33-9, Temiverine hydrochloride
- RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
- (epoxy-steroidal aldosterone antagonist and calcium channel blocker combination therapy for treatment of congestive heart failure and other cardiovascular disorders)

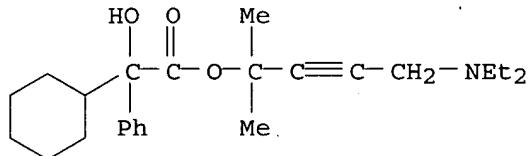
RN 104454-71-9 HCPLUS

CN 2-Oxazolidinone, 3-[3-(hexahydro-1H-azepin-1-yl)propyl]-4-(2-methylpropyl)-5-phenyl-, (4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 129927-33-9 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)

● HCl

L61 ANSWER 31 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:10123 HCPLUS

DOCUMENT NUMBER: 136:64091

TITLE: Method and system for predicting pharmacokinetic properties

INVENTOR(S): Hattori, Kazunari; Shimada, Kaore; Uchiyama, Mamoru

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: Eur. Pat. Appl., 27 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1167969	A2	20020102	EP 2001-304648	20010525 <-
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2003069698	A1	20030410	US 2001-876767	20010607 <-
JP 2003014728	A2	20030115	JP 2001-179774	20010614 <-
PRIORITY APPLN. INFO.:			US 2000-211864P	P 20000614

AB This invention provides a method for predicting pharmacokinetic properties of mols. comprising the steps of: (a) preparing 2D-structures of mols. used as a training set; (b) constructing a 2D-fingerprint by counting the number of structural descriptors that potentially relate to a pharmacokinetic property, either manually or automatically using internally developed macro; wherein said structural descriptors consist of predefined 20 to 80 atoms/fragments or substructures; (c) analyzing the obtained 2D-fingerprint by a statistical anal. method to correlate with the pharmacokinetic property of the mol. to yield a quant. structure-property relation (QSPR) model; and (d) calculating the pharmacokinetic property of a trial mol. using the above obtained QSPR model. A system for this invention is also provided. According to this method and system, it is possible to predict pharmacokinetic properties of mols. prior to synthesis, without labor-intensive and time-consuming experimentation.

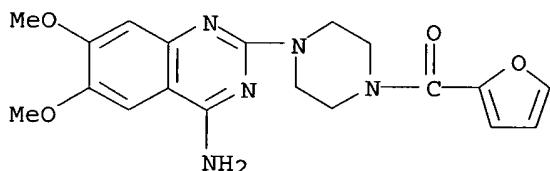
IT 19216-56-9, Prazosin 122384-10-5

384329-56-0 384329-57-1

RL: PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study)
(method and system for predicting pharmacokinetic properties)

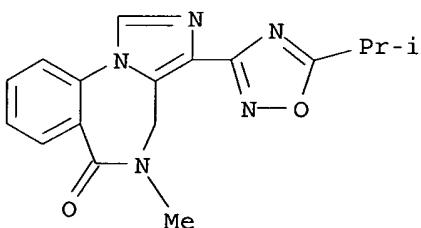
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-
(9CI) (CA INDEX NAME)



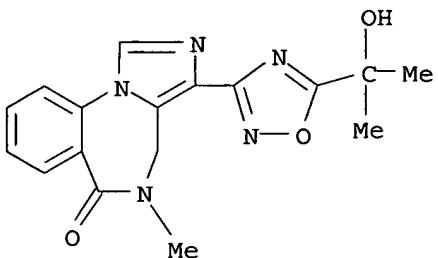
RN 122384-10-5 HCAPLUS

CN 6H-Imidazo[1,5-a][1,4]benzodiazepin-6-one, 4,5-dihydro-5-methyl-3-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]- (9CI) (CA INDEX NAME)



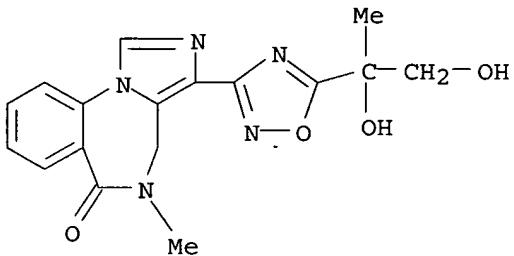
RN 384329-56-0 HCAPLUS

CN 6H-Imidazo[1,5-a][1,4]benzodiazepin-6-one, 4,5-dihydro-3-[5-(1-hydroxy-1-methylethyl)-1,2,4-oxadiazol-3-yl]-5-methyl- (9CI) (CA INDEX NAME)



RN 384329-57-1 HCPLUS

CN 6H-Imidazo[1,5-a][1,4]benzodiazepin-6-one, 3-[5-(1,2-dihydroxy-1-methylethyl)-1,2,4-oxadiazol-3-yl]-4,5-dihydro-5-methyl- (9CI) (CA INDEX NAME)



L61 ANSWER 32 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:935434 HCPLUS

DOCUMENT NUMBER: 136:58848

TITLE: Curative method for pathologic syndromes and homeopathic medicinal preparations

INVENTOR(S): Epshtein, Oleg Iliich; Kolyadko, Tamara Mikhailovna; Shtark, Mark Borisovich

PATENT ASSIGNEE(S): Russia

SOURCE: PCT Int. Appl., 100 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Russian

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097842	A1	20011227	WO 2001-RU239	20010619 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
RU 2181297	C2	20020420	RU 2000-115594	20000620 <--
CA 2413358	AA	20011227	CA 2001-2413358	20010619 <--
AU 2001069646	A5	20020102	AU 2001-69646	20010619 <--
EP 1295606	A1	20030326	EP 2001-948169	20010619 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003099636 A1 20030529 US 2002-311666 20021217 <--

PRIORITY APPLN. INFO.: RU 2000-115594 A 20000620
WO 2001-RU239 W 20010619

AB The inventive curative method for a pathol. syndrome consists in inserting into an organism activated forms of minute antibody doses which are produced by means of a repeated successive dilution and an external action carried out on an antigen, e.g. a substance or medicinal preparation influencing a mechanism forming said pathol. syndrome. The inventive medicinal preparation for curing the pathol. syndrome comprises an activated form of minute doses of monoclonal, polyclonal or natural antibodies. Said antibodies are produced by means of a repeated successive dilution and an external action, preferably using homeopathic technol., which is carried out on an antigen, e.g. a substance or medicinal preparation directly promoting the formation of the pathol. syndrome or participating in regulating mechanisms for the formation thereof. Activated forms of minute doses of antibodies to the antigens of an exogenic and endogenic nature, autoantigens and fetal antigens, are used. Anti-idiotypic antibodies are also used.

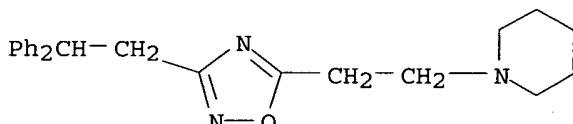
IT 982-43-4, Libexin 19216-56-9, Prazosin

106463-17-6, Omnic

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; curative method for pathol. syndromes and homeopathic medicinal prepn.)

RN 982-43-4 HCAPLUS

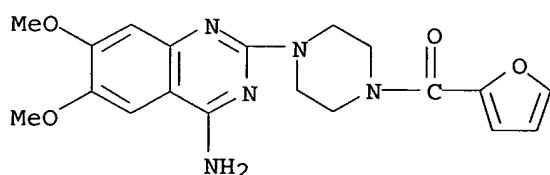
CN Piperidine, 1-[2-[3-(2,2-diphenylethyl)-1,2,4-oxadiazol-5-yl]ethyl]-, monohydrochloride (8CI, 9CI) (CA INDEX NAME)



● HCl

RN 19216-56-9 HCAPLUS

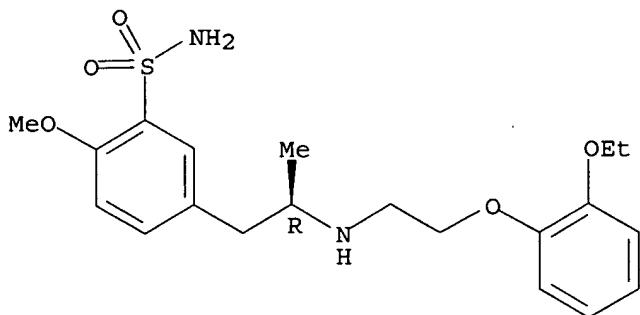
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



RN 106463-17-6 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)

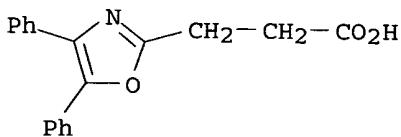
Absolute stereochemistry. Rotation (-).



● HCl

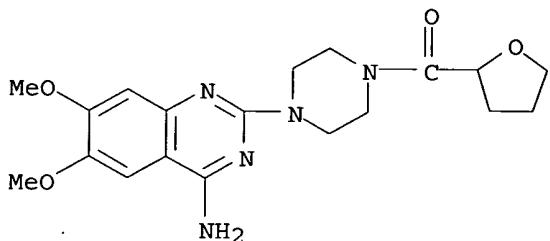
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 33 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:884254 HCPLUS
 DOCUMENT NUMBER: 136:160858
 TITLE: Top 200 medicines: can new actions be discovered through computer-aided prediction?
 AUTHOR(S): Poroikov, V.; Akimov, D.; Shabelnikova, E.; Filimonov, D.
 CORPORATE SOURCE: Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow, 119832, Russia
 SOURCE: SAR and QSAR in Environmental Research (2001), 12(4), 327-344
 CODEN: SQERED; ISSN: 1062-936X
 PUBLISHER: Gordon & Breach Science Publishers
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Computer-aided prediction of the biol. activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacol. effects were found in the predicted activity spectra in 93.2% of cases. Addnl., the probability of some supplementary effects was also predicted to be significant, including angiogenesis inhibition, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, etc. These predictions, if confirmed exptl., may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R & D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clin. use which become apparent only in a small part of the population and require addnl. precautions.
 IT 21256-18-8, Oxaprozin 63590-64-7, Terazosin
 74191-85-8, Doxazosin
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (drug discovery through computer-aided prediction)
 RN 21256-18-8 HCPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



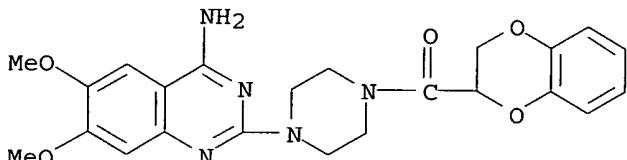
RN 63590-64-7 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 34 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:830464 HCPLUS

DOCUMENT NUMBER: 136:128586

TITLE: Synthesis and structure-activity relationships in a set of new antimuscarinic agents

AUTHOR(S): De Amici, Marco; Conti, Paola; Vistoli, Giulio; Carrea, Giacomo; Ottolina, Gianluca; De Micheli, Carlo

CORPORATE SOURCE: Istituto di Chimica Farmaceutica e Tossicologica, Universita di Milano, Milan, 42-20131, Italy

SOURCE: Medicinal Chemistry Research (2001), 10(9), 615-633

PUBLISHER: CODEN: MCREEB; ISSN: 1054-2523

DOCUMENT TYPE: Birkhaeuser Boston

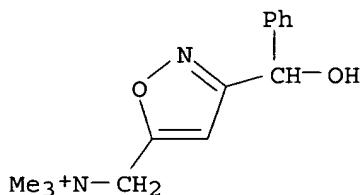
LANGUAGE: English

OTHER SOURCE(S): CASREACT 136:128586

AB Three quaternary ammonium salts, related to muscarine and muscarone, were designed as antimuscarinic agents and synthesized by means of a iodoetherification reaction carried out on an unsatd. diol. The structurally related furanone together with isoxazoles and Δ^2 -isoxazolines were in turn obtained via 1,3-dipolar cycloaddn. of

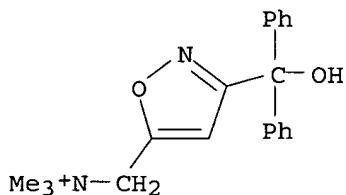
benzoylformonitrile oxide to suitable alkynes and alkenes. The new derivs. were tested in vitro for antimuscarinic activity at guinea pig atria (M2) and at 2 different M3 tissue preps. (rat jejunum and guinea pig bladder). Selected compds. were also examined for binding activity at M1, M2, and M3 muscarinic receptors. The major part of the derivs. under study behaved as highly potent, though non selective, muscarinic antagonists. Selected geometrical parameters capable of predicting the selectivity of new antagonists for M2 vs. M3 receptors were proposed.

- IT 392699-86-4P 392699-87-5P 392699-88-6P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (synthesis and structure-activity relationships in a set of new antimuscarinic agents)
- RN 392699-86-4 HCPLUS
 CN 5-Isoxazolemethanaminium, 3-(hydroxyphenylmethyl)-N,N,N-trimethyl-, iodide (9CI) (CA INDEX NAME)



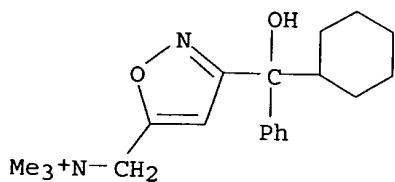
● I⁻

- RN 392699-87-5 HCPLUS
 CN 5-Isoxazolemethanaminium, 3-(hydroxydiphenylmethyl)-N,N,N-trimethyl-, iodide (9CI) (CA INDEX NAME)



● I⁻

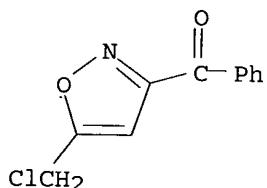
- RN 392699-88-6 HCPLUS
 CN 5-Isoxazolemethanaminium, 3-(cyclohexylhydroxyphenylmethyl)-N,N,N-trimethyl-, iodide (9CI) (CA INDEX NAME)



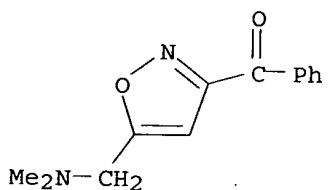
● I -

IT 220867-82-3P 392699-95-5P 392699-97-7P
 392699-99-9P 392700-01-5P 392700-05-9P
 392700-07-1P 392700-09-3P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (synthesis and structure-activity relationships in a set of new
 antimuscarinic agents)

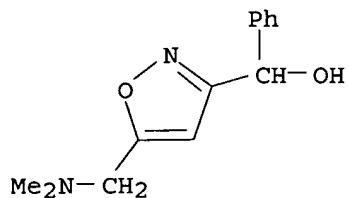
RN 220867-82-3 HCAPLUS
 CN Methanone, [5-(chloromethyl)-3-isoxazolyl]phenyl- (9CI) (CA INDEX NAME)



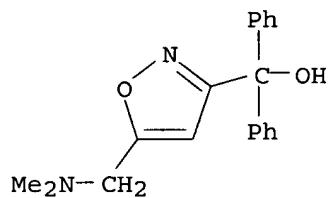
RN 392699-95-5 HCAPLUS
 CN Methanone, [5-[(dimethylamino)methyl]-3-isoxazolyl]phenyl- (9CI) (CA
 INDEX NAME)



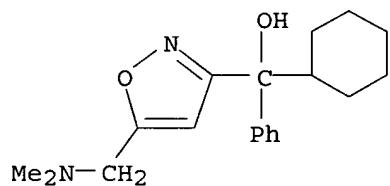
RN 392699-97-7 HCAPLUS
 CN 3-Isoxazolemethanol, 5-[(dimethylamino)methyl]-alpha-phenyl- (9CI) (CA
 INDEX NAME)



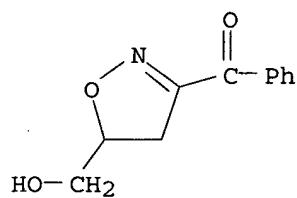
RN 392699-99-9 HCPLUS
CN 3-Isoxazolemethanol, 5-[(dimethylamino)methyl]-α,α-diphenyl-
(9CI) (CA INDEX NAME)



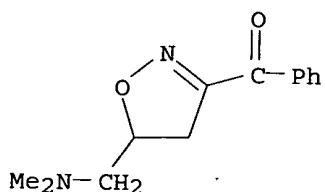
RN 392700-01-5 HCPLUS
CN 3-Isoxazolemethanol, α-cyclohexyl-5-[(dimethylamino)methyl]-α-phenyl- (9CI) (CA INDEX NAME)



RN 392700-05-9 HCPLUS
CN Methanone, [4,5-dihydro-5-(hydroxymethyl)-3-isoxazolyl]phenyl- (9CI) (CA INDEX NAME)

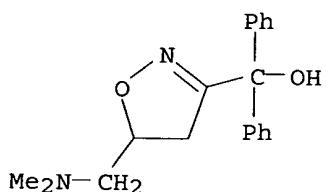


RN 392700-07-1 HCPLUS
CN Methanone, [5-[(dimethylamino)methyl]-4,5-dihydro-3-isoxazolyl]phenyl-
(9CI) (CA INDEX NAME)



RN 392700-09-3 HCPLUS

CN 3-Isoxazolemethanol, 5-[(dimethylamino)methyl]-4,5-dihydro-alpha,alpha-diphenyl- (9CI) (CA INDEX NAME)

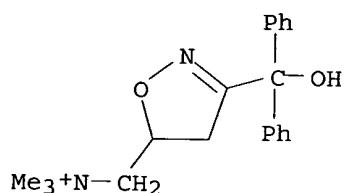


IT 392699-89-7P

RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and structure-activity relationships in a set of new
antimuscarinic agents)

RN 392699-89-7 HCPLUS

CN 5-Isoxazolemethanaminium, 4,5-dihydro-3-(hydroxydiphenylmethyl)-N,N,N-trimethyl-, iodide (9CI) (CA INDEX NAME)



● I -

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 35 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:816444 HCPLUS

DOCUMENT NUMBER: 135:352829

TITLE: Combination therapeutic compositions containing benzene compounds

INVENTOR(S): Jaen, Juan C.; Chen, Jin-Long

PATENT ASSIGNEE(S): Tularik Inc., USA

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

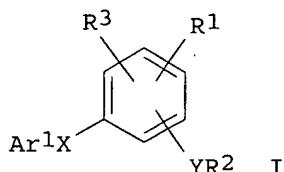
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082916	A2	20011108	WO 2001-US14393	20010502 <--
WO 2001082916	A3	20020704		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002037928	A1	20020328	US 2001-847887	20010502 <--
US 6653332	B2	20031125		
US 2004259918	A1	20041223	US 2003-456932	20030605
US 2006035928	A1	20060216	US 2005-258817	20051026
PRIORITY APPLN. INFO.:			US 2000-201613P	P 20000503
			US 2001-847887	A1 20010502
			US 2003-456932	A1 20030605

OTHER SOURCE(S) : MARPAT 135:352829

GI



- AB The present invention provides pharmaceutical compns. and methods for the treatment of diabetes mellitus using combination therapy. The compns. relate to a benzene compound and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, α -glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of benzene compound with antidiabetic agent where the two components are delivered in a simultaneous manner, where the benzene compound is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the benzene compound. For example, the benzene compound (I) was synthesized using a 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile (0.457 g) in methylene chloride to which was added 2,4-dichlorobenzensulfonyl chloride (0.456 g), followed by pyridine (150 μ L). The reaction progress was monitored by TLC, and upon completion the solvent was removed under vacuum. The resulting residue was partitioned between methylene chloride and water. The organic layer was drawn off and concentrated. The residue was triturated with ether to provide 0.447 g of I as a white solid, m.p. 154-156°.
- IT 19216-56-9, Prazocine 103787-97-9, BM 131246
103788-05-2, AD-5075 141200-24-0, Darglitazone

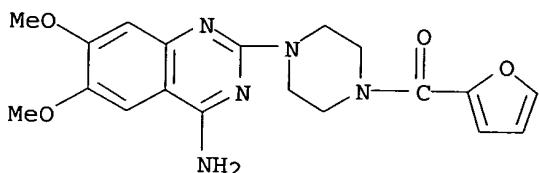
170861-63-9, JTT-501

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(benzene compds. in combination therapy for diabetes and diabetes-related disorders)

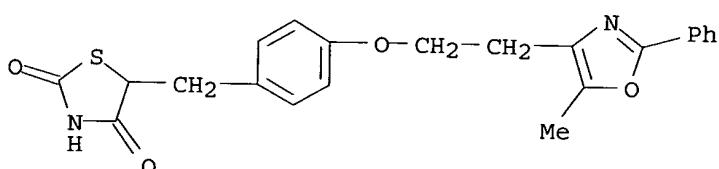
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



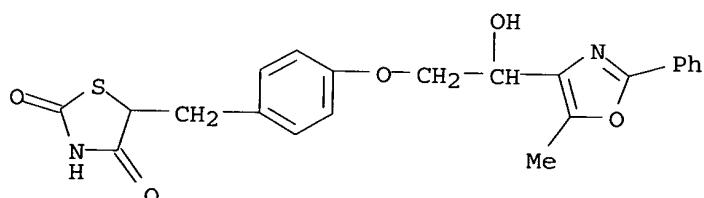
RN 103787-97-9 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-(9CI) (CA INDEX NAME)



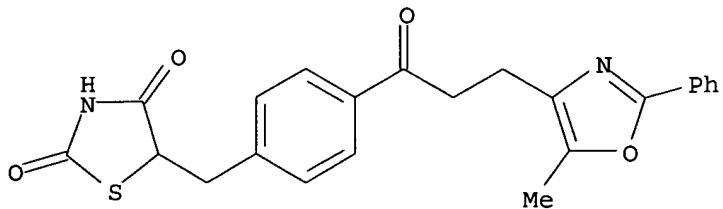
RN 103788-05-2 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-(9CI) (CA INDEX NAME)



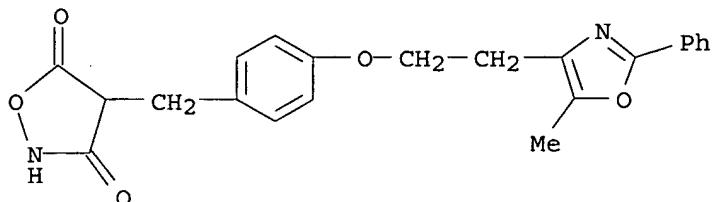
RN 141200-24-0 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-(9CI) (CA INDEX NAME)



RN 170861-63-9 HCAPLUS

CN 3,5-Isoxazolidinedione, 4-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 36 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:658077 HCAPLUS

DOCUMENT NUMBER: 135:205580

TITLE: Method for inhibiting or treating chemotherapy-induced hair loss

INVENTOR(S): Atwal, Karnail S.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: U.S. Pat. Appl. Publ., 8 pp., Cont.-in-part of U.S. Ser. No. 447,002.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001020038	A1	20010906	US 2001-805347	20010313 <--
US 6458835	B2	20021001		
US 6013668	A	20000111	US 1998-119884	19980721 <--
ZA 9807220	A	20000214	ZA 1998-7220	19980812 <--
US 6472427	B1	20021029	US 1999-447002	19991122 <--
US 6262122	B1	20010717	US 2000-615345	20000712 <--
PRIORITY APPLN. INFO.:				
			US 1997-55568P	P 19970813
			US 1998-71364P	P 19980115
			US 1998-119884	A1 19980721
			US 1999-447002	A2 19991122

AB A method for inhibiting hair loss and/or promoting hair growth in chemotherapy and/or radiation therapy patients wherein the (R)-enantiomer of 4-[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile is administered prior to, simultaneous with and/or after chemotherapy and/or radiation treatment. There was a remarkable difference between the 1-(R)-enantiomer and the 2-(S)-enantiomer in their effect on hair follicle

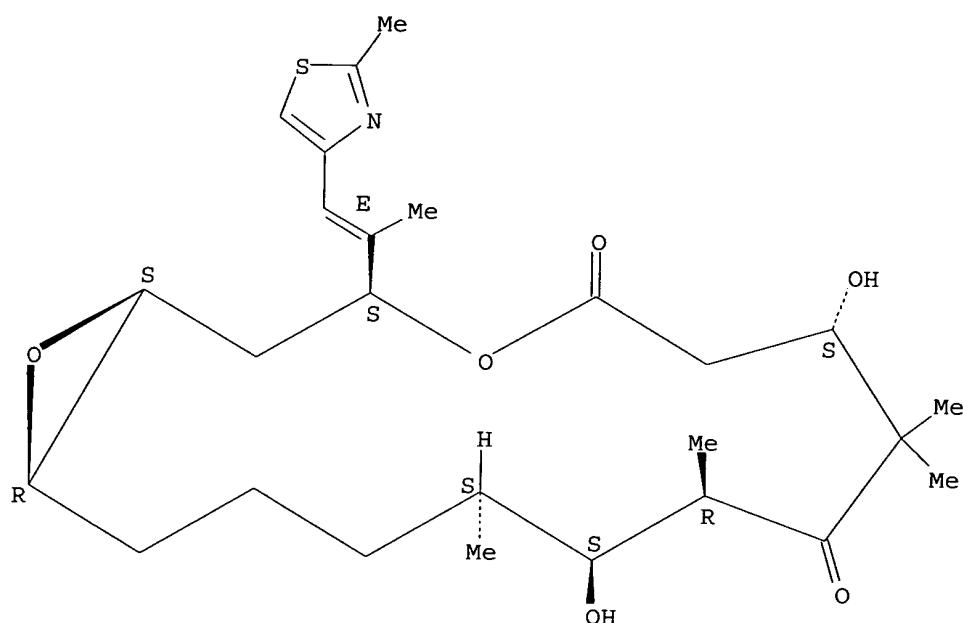
stimulation; in particular the (R)-enantiomer had a faster onset of action compared to the corresponding (S)-enantiomer. While the IC₅₀ for vasorelaxant potency of the (R)-enantiomer is 47±17 nM vs. 157±35 nM for the (S)-enantiomer, the hair growth promoting ability of the (R)-enantiomer for producing hair growth within 11 days of treatment is 8 times greater than the corresponding (S)-enantiomer.

IT 152044-53-6, Epothilone A 152044-54-7, Epothilone B
 186692-73-9, Epothilone C 189453-10-9, Epothilone D
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antitumor; method for inhibiting or treating chemotherapy-induced hair loss)

RN 152044-53-6 HCAPLUS

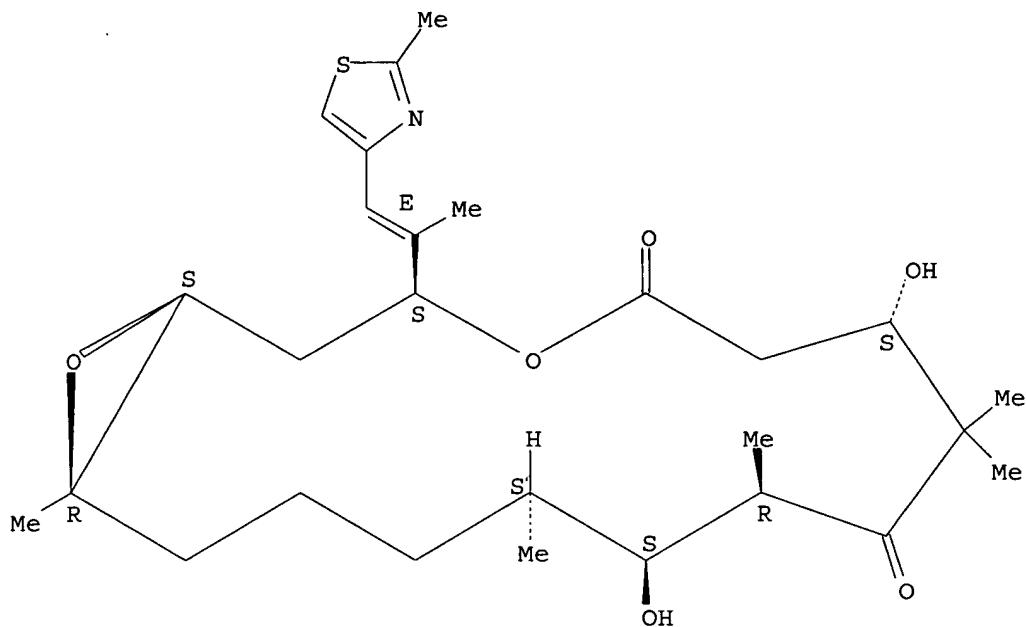
CN 4,17-Dioxabicyclo[4.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12-tetramethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



CN 4,17-Dioxabicyclo[4.1.0]heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)- (9CI) (CA INDEX NAME)

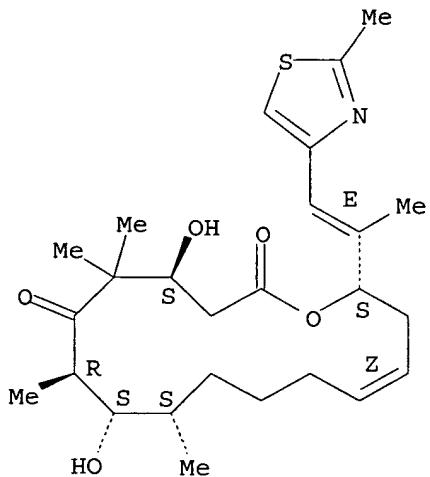
Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



RN 186692-73-9 HCPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

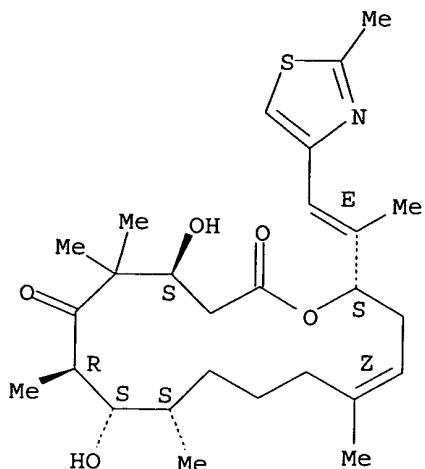
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



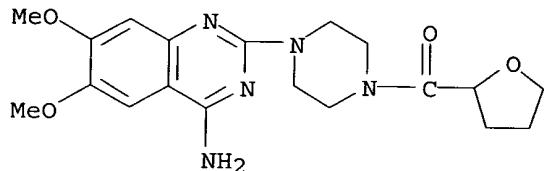
RN 189453-10-9 HCPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



IT 63074-08-8, Terazosin hydrochloride
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as hair growth promoter, in combination; method for inhibiting or treating chemotherapy-induced hair loss)
 RN 63074-08-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L61 ANSWER 37 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:396644 HCAPLUS
 DOCUMENT NUMBER: 135:24671
 TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
 INVENTOR(S): Patel, Manesh V.; Chen, Feng-jing
 PATENT ASSIGNEE(S): Lipocene, Inc., USA
 SOURCE: PCT Int. Appl., 107 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 13
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001037808	A1	20010531	WO 2000-US32255	20001122 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6248363	B1	20010619	US 1999-447690	19991123 <--
CA 2391923	AA	20010531	CA 2000-2391923	20001122 <--
EP 1233756	A1	20020828	EP 2000-980761	20001122 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003517470	T2	20030527	JP 2001-539423	20001122 <--
PRIORITY APPLN. INFO.:			US 1999-447690	A 19991123
			WO 2000-US32255	W 20001122

AB The present invention provides solid pharmaceutical compns. for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or sep. administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritionals, cosmeceuticals and diagnostic agents. A composition contained glyburide 1, PEG 40 stearate 33, glycerol monolaurate 17, and nonpareil seed 80 g.

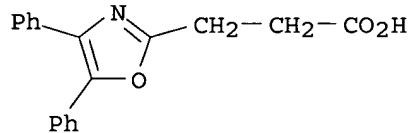
IT 21256-18-8, Oxaprozin 106133-20-4, Tamsulosin

139264-17-8, Zolmitriptan

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in
pharmaceutical compns.)

RN 21256-18-8 HCPLUS

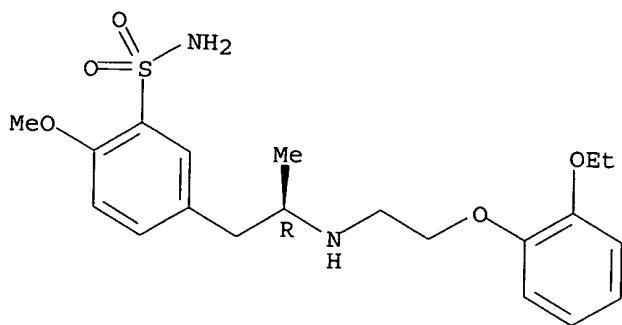
CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[(2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

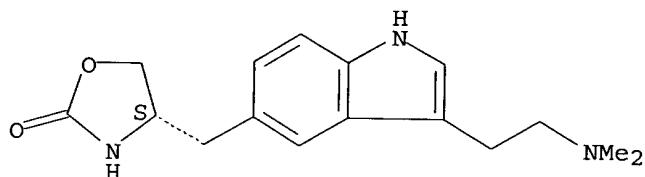
Absolute stereochemistry. Rotation (-).



RN 139264-17-8 HCAPLUS

CN 2-Oxazolidinone, 4-[(3-[2-(dimethylamino)ethyl]-1H-indol-5-yl)methyl]-,
(4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 38 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:338762 HCAPLUS

DOCUMENT NUMBER: 134:362292

TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile

INVENTOR(S): Farr, Spencer

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA

SOURCE: PCT Int. Appl., 222 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

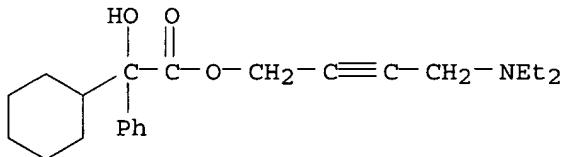
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

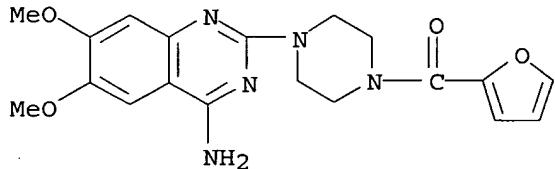
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103 <--
WO 2001032928	A3	20020725		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			US 1999-165398P	P 19991105

US 2000-196571P P 20000411

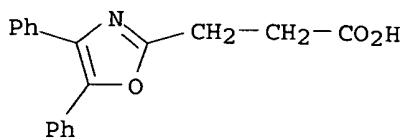
- AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.
- IT 5633-20-5, Oxybutynin 19216-56-9,
Prazosin 21256-18-8, Oxaprozin 63590-64-7,
Terazosin 74191-85-8, Doxazosin
97519-39-6, Ceftibuten 106133-20-4, Tamsulosin
124937-51-5, Tolterodine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)
- RN 5633-20-5 HCAPLUS
- CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



- RN 19216-56-9 HCAPLUS
- CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)

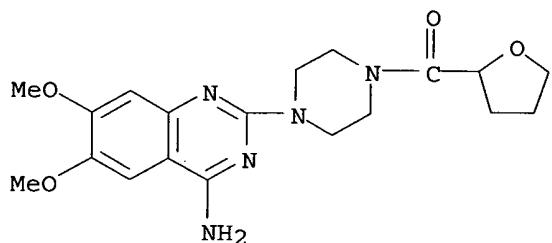


- RN 21256-18-8 HCAPLUS
- CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



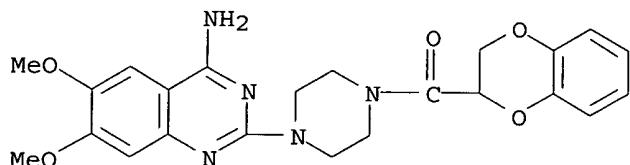
RN 63590-64-7 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)

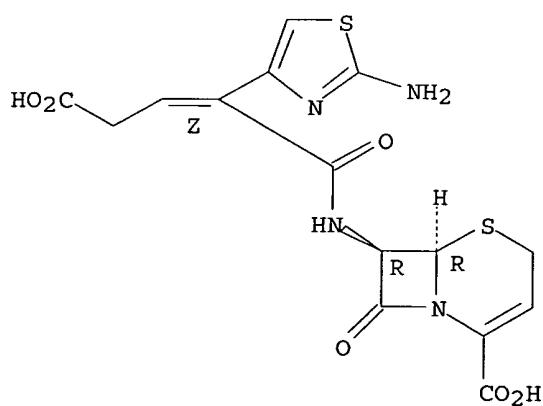


RN 97519-39-6 HCAPLUS

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[((2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl)amino]-8-oxo-, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

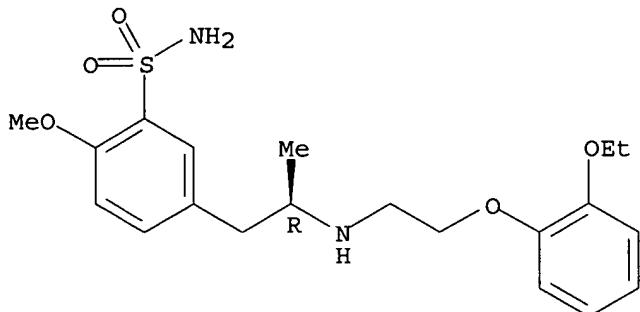
Double bond geometry as shown.



RN 106133-20-4 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

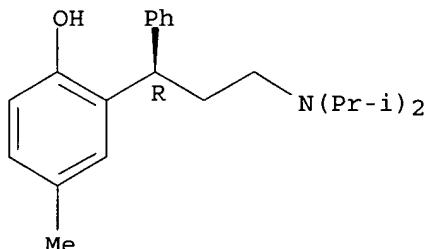
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCAPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L61 ANSWER 39 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:283949 HCAPLUS

DOCUMENT NUMBER: 134:311218

TITLE: Synthesis and use of heterocyclic sodium/proton exchange inhibitors

INVENTOR(S): Ahmad, Saleem; Wu, Shung C.; O'Neil, Steven V.; Ngu, Khehyong; Atwal, Karnail S.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 221 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027107	A2	20010419	WO 2000-US27461	20001002 <--
WO 2001027107	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

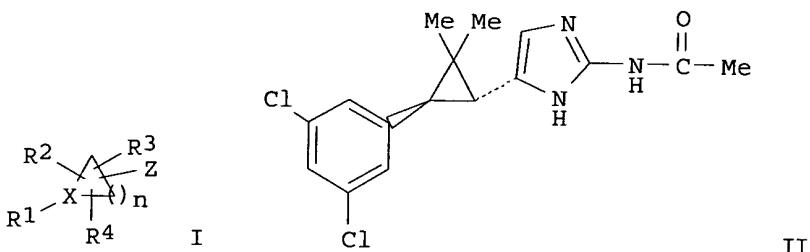
US 6887870	B1	20050503	US 2000-669298	20000925
CA 2388813	AA	20010419	CA 2000-2388813	20001002 <--
EP 1224183	A2	20020724	EP 2000-968723	20001002 <--
EP 1224183	B1	20051228		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL

BR 2000014725	A	20030617	BR 2000-14725	20001002	<--
JP 2003527331	T2	20030916	JP 2001-530325	20001002	<--
NZ 517668	A	20040924	NZ 2000-517668	20001002	
AT 314364	E	20060115	AT 2000-968723	20001002	
ES 2254236	T3	20060616	ES 2000-968723	20001002	
ZA 2002002479	A	20040727	ZA 2002-2479	20020327	
NO 2002001717	A	20020610	NO 2002-1717	20020411	<--
US 2005137216	A1	20050623	US 2005-46993	20050121	

PRIORITY APPLN. INFO.: 112 20000023 US 2003-46993 20050131
US 1999-158755P P 19991012
US 2000-669298 A3 20000925
WO 2000-US27461 W 20001002

OTHER SOURCE(S) : MARPAT 134:311218
GI



AB Compds. of formula I [wherein; n is 1-5; X is N or CR₅, where R₅ is H, halo, alkenyl, alkynyl, alkoxy, alkyl, aryl or heteroaryl; Z is a heteroaryl group; R₁ is H, alk(en)ynyl, alk(enyl)(ynyl)oxy, (aryl or alkyl)Si, cycloalk(en)yl, (aryl)amino, aryl(alkyl), cycloheteroaryl, etc.; R₂, R₃ and R₄ are any of the groups set out for R₁ and optionally substituted with 1 to 5 substituents which may be the same or different and when X is N, R₁ is preferably aryl or heteroaryl] are claimed. Several hundred examples are disclosed. Synthesis of II proceeds via cyclopropanation of the cinnamate derived from the olefination between 3,5-dichlorobenzaldehyde and t-butyldiethylphosphonoacetate. The intermediate tert-Bu ester is converted to the corresponding α -chloroketone and reacted with acetyl guanidine to provide II in a total of 5 steps. Compds. I are said to be sodium/proton exchange inhibitors (NHE). Pharmaceutical combinations are claimed using I and certain antihypertensive agents, β -adrenergic agonists, hypolipidemic agents, antidiabetic agents, antiobesity agents, etc. Compds. I are useful as antianginal and cardioprotective agents and provide a method for preventing or treating angina pectoris, cardiac dysfunction, myocardial necrosis, and arrhythmia.

IT 19237-84-4, Prazosin hydrochloride 170861-63-9
, JTT-501 196808-45-4, GI-262570 335149-19-4, GW

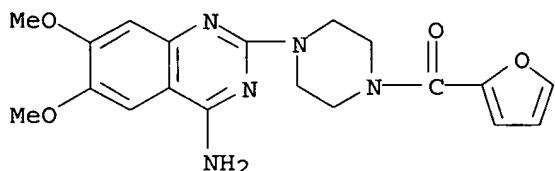
409544

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmaceuticals also containing; synthesis and use of heterocyclic sodium/proton exchange inhibitors)

RN 19237-84-4 HCPLUS

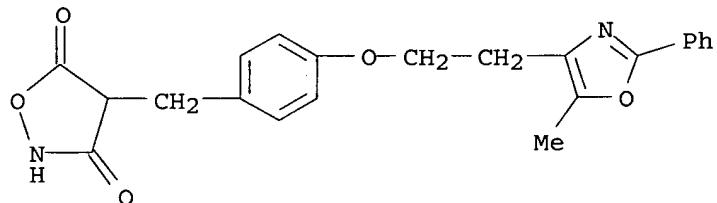
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 170861-63-9 HCPLUS

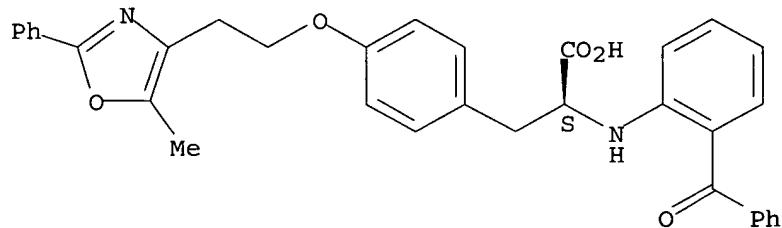
CN 3,5-Isoxazolidinedione, 4-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 196808-45-4 HCPLUS

CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

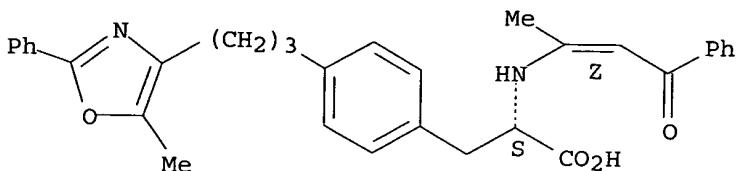


RN 335149-19-4 HCPLUS

CN L-Phenylalanine, N-[(1Z)-1-methyl-3-oxo-3-phenyl-1-propenyl]-4-[3-(5-methyl-2-phenyl-4-oxazolyl)propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

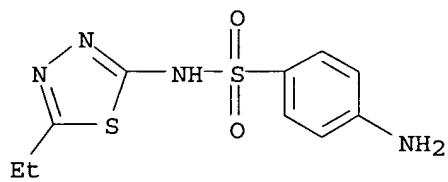


L61 ANSWER 40 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:137173 HCPLUS
 DOCUMENT NUMBER: 134:178396
 TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
 INVENTOR(S): Del Soldato, Piero
 PATENT ASSIGNEE(S): Nicox S.A., Fr.
 SOURCE: PCT Int. Appl., 94 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012584	A2	20010222	WO 2000-EP7225	20000727 <--
WO 2001012584	A3	20020829		
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2381409	AA	20010222	CA 2000-2381409	20000727 <--
BR 2000013264	A	20020416	BR 2000-13264	20000727 <--
EP 1252133	A2	20021030	EP 2000-953102	20000727 <--
EP 1252133	B1	20050608		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003515526	T2	20030507	JP 2001-516885	20000727 <--
NZ 516889	A	20041029	NZ 2000-516889	20000727
AU 781643	B2	20050602	AU 2000-65670	20000727
AT 297375	E	20050615	AT 2000-953102	20000727
EP 1593664	A1	20051109	EP 2005-104064	20000727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY				
RU 2264383	C2	20051120	RU 2002-103509	20000727
ES 2243292	T3	20051201	ES 2000-953102	20000727
NZ 535559	A	20051223	NZ 2000-535559	20000727
ZA 2002000628	A	20030423	ZA 2002-628	20020123 <--
NO 2002000623	A	20020409	NO 2002-623	20020208 <--
AU 2005202824	A1	20050721	AU 2005-202824	20050628
PRIORITY APPLN. INFO.:			IT 1999-MI1817	A 19990812
			EP 2000-953102	A3 20000727
			WO 2000-EP7225	W 20000727

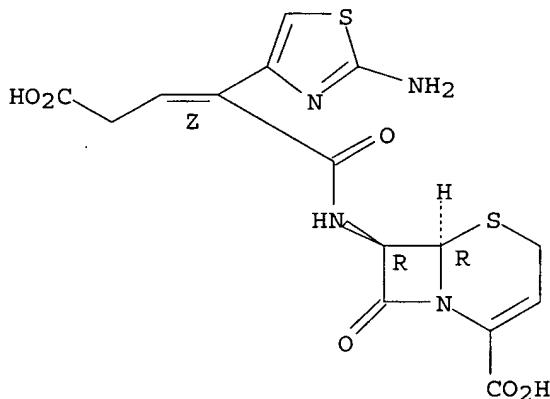
OTHER SOURCE(S): MARPAT 134:178396
 AB Compds. or their salts of general formula (I): A-B-N(O)s wherein: s is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 = (CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB -X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT 94-19-9, Sulfaethidole 97519-39-6, Ceftibuten
 105889-45-0, Cefcapene pivoxil
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (antibiotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)
 RN 94-19-9 HCPLUS
 CN Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (9CI) (CA INDEX NAME)



RN 97519-39-6 HCPLUS
 CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 7-[(2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-,
 (6R,7R)- (9CI) (CA INDEX NAME)

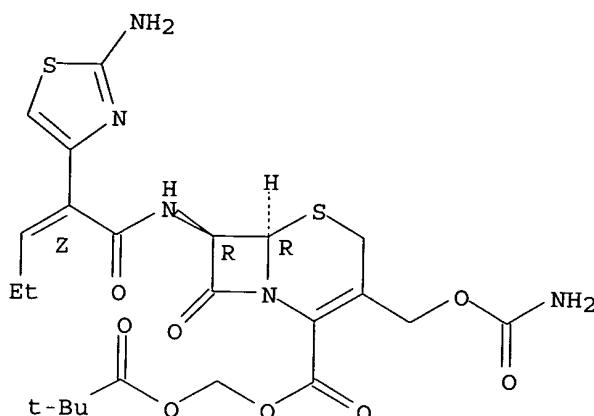
Absolute stereochemistry.
 Double bond geometry as shown.



RN 105889-45-0 HCPLUS
 CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 3-[(aminocarbonyl)oxy]methyl]-7-[(2Z)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl]amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, (6R,7R)-

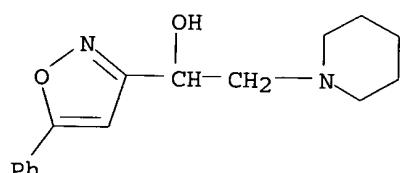
(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



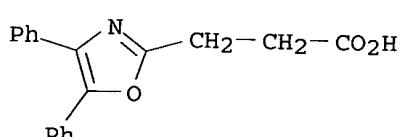
IT 2055-44-9, Perisoxal 21256-18-8, Oxaprozin
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (antiinflammatory; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 2055-44-9 HCPLUS

CN 1-Piperidineethanol, α -(5-phenyl-3-isoxazolyl)- (7CI, 8CI, 9CI) (CA INDEX NAME)

RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)

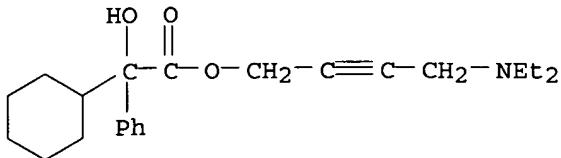


IT 5633-20-5, Oxybutynin 129927-33-9, NS-21

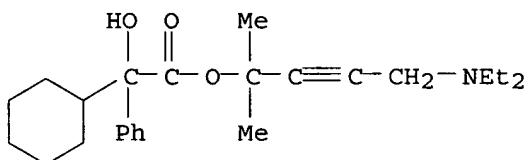
RL: RCT (Reactant); RACT (Reactant or reagent)
 (bronchodilator; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 5633-20-5 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



RN 129927-33-9 HCPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, hydrochloride (9CI) (CA
 INDEX NAME)



● HCl

L61 ANSWER 41 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:861473 HCPLUS
 DOCUMENT NUMBER: 134:32972
 TITLE: Porous drug matrixes containing polymers and sugars
 and methods of their manufacture
 INVENTOR(S): Straub, Julie; Bernstein, Howard; Chickering, Donald
 E., III; Khatak, Sarwat; Randall, Greg
 PATENT ASSIGNEE(S): Acusphere, Inc., USA
 SOURCE: PCT Int. Appl., 45 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072827	A2	20001207	WO 2000-US14578	20000525 <--
WO 2000072827	A3	20010125		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6395300	B1	20020528	US 1999-433486	19991104 <--
CA 2371836	AA	20001207	CA 2000-2371836	20000525 <--
CA 2371836	C	20060131		
EP 1180020	A2	20020220	EP 2000-939365	20000525 <--

EP 1180020	B1	20051214		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
BR 2000010984	A	20020430	BR 2000-10984	20000525 <--
JP 2003500438	T2	20030107	JP 2000-620939	20000525 <--
NZ 516083	A	20030829	NZ 2000-516083	20000525 <--
AU 768022	B2	20031127	AU 2000-54459	20000525
AT 312601	E	20051215	AT 2000-939365	20000525
EP 1642572	A1	20060405	EP 2005-27194	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
ES 2250141	T3	20060416	ES 2000-939365	20000525
US 2002041896	A1	20020411	US 2001-798824	20010302 <--
US 6610317	B2	20030826		
NO 2001005753	A	20020128	NO 2001-5753	20011126 <--
ZA 2001010347	A	20030730	ZA 2001-10347	20011218 <--
PRIORITY APPLN. INFO.:			US 1999-136323P	P 19990527
			US 1999-158659P	P 19991008
			US 1999-433486	A 19991104
			US 2000-186310P	P 20000302
			EP 2000-939365	A3 20000525
			WO 2000-US14578	W 20000525

AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form,

preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a process that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in

a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solns., and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Paclitaxel or docetaxel can be provided in a porous matrix form, which allows the drug to be formulated without solubilizing agents and administered as a bolus. For example, a nifedipine-loaded organic solution was prepared by dissolving 9.09 g of PEG 3350, 2.27 g of nifedipine, and 0.009 g of lecithin in 182 mL of methylene chloride. An aqueous solution was

prepared by dissolving 3.27 g of NH₄HCO₃ and 0.91 g of PEG 3350 in 1.82 mL of water. The aqueous and organic solns. were homogenized and resulting emulsion

was spray dried. A suspension of the porous nifedipine drug matrix was prepared in 5% dextrose solution at a concentration of 2.5 mg/mL. A bolus injection

of the suspension was tolerated when administrated to dogs.

IT 21256-18-8, Oxaprozin 77883-43-3, Doxazosin

mesylate 106463-17-6, Tamsulosin hydrochloride

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

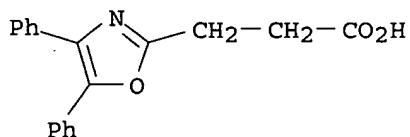
(preparation of porous matrixes containing hydrophilic polymers and sugars

for

enhancement of drug dissoln.)

RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



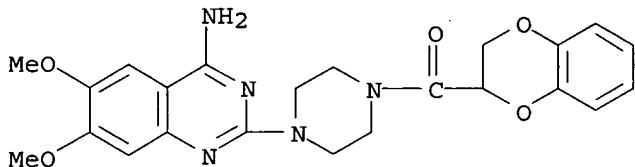
RN 77883-43-3 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 74191-85-8

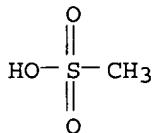
CMF C23 H25 N5 O5



CM 2

CRN 75-75-2

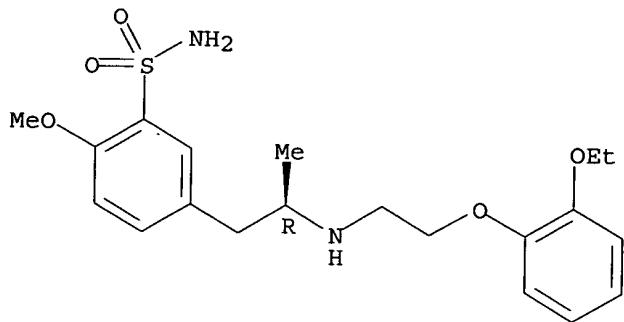
CMF C H4 O3 S



RN 106463-17-6 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L61 ANSWER 42 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:742057 HCPLUS

DOCUMENT NUMBER: 133:309791

TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction

INVENTOR(S): Del Soldato, Piero

PATENT ASSIGNEE(S): Nicox S.A., Fr.

SOURCE: PCT Int. Appl., 140 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061541	A2	20001019	WO 2000-EP3239	20000411 <--
WO 2000061541	A3	20010927		
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IT 1311923	B1	20020320	IT 1999-MI752	19990413 <--
CA 2370425	AA	20001019	CA 2000-2370425	20000411 <--
BR 2000009703	A	20020108	BR 2000-9703	20000411 <--
EP 1169298	A2	20020109	EP 2000-926870	20000411 <--
EP 1169298	B1	20060104		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
JP 2002541236	T2	20021203	JP 2000-610818	20000411 <--
TR 200102928	T2	20021223	TR 2001-2928	20000411 <--
NZ 514270	A	20040227	NZ 2000-514270	20000411
RU 2237057	C2	20040927	RU 2001-127574	20000411
AU 777579	B2	20041021	AU 2000-45474	20000411
AT 315021	E	20060215	AT 2000-926870	20000411
ZA 2001008126	A	20030403	ZA 2001-8126	20011003 <--

NO 2001004928	A 20011213	NO 2001-4928	20011010 <--
US 6987120	B1 20060117	US 2001-926322	20011015
US 2006030605	A1 20060209	US 2005-234084	20050926
PRIORITY APPLN. INFO.:		IT 1999-MI752	A 19990413
		WO 2000-EP3239	W 20000411
		US 2001-926322	A3 20011015

OTHER SOURCE(S): MARPAT 133:309791

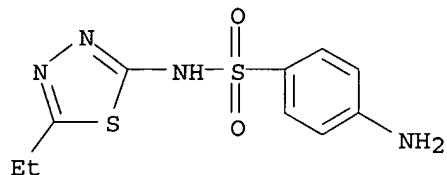
AB Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT 94-19-9, Sulfaethidole 97519-39-6, Ceftibuten
105889-45-0, Cefcapene pivoxil

RL: RCT (Reactant); RACT (Reactant or reagent)
(antibiotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 94-19-9 HCPLUS

CN Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (9CI) (CA INDEX NAME)

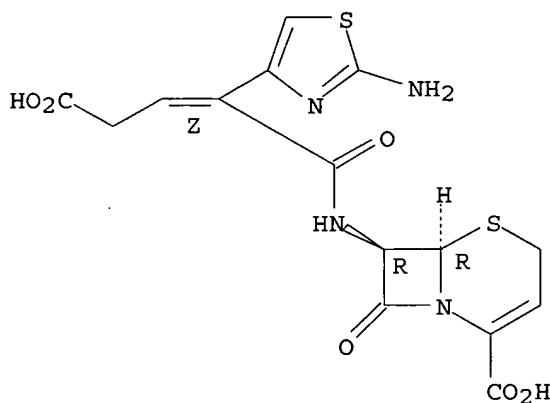


RN 97519-39-6 HCPLUS

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
7-[(2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-,
(6R,7R) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

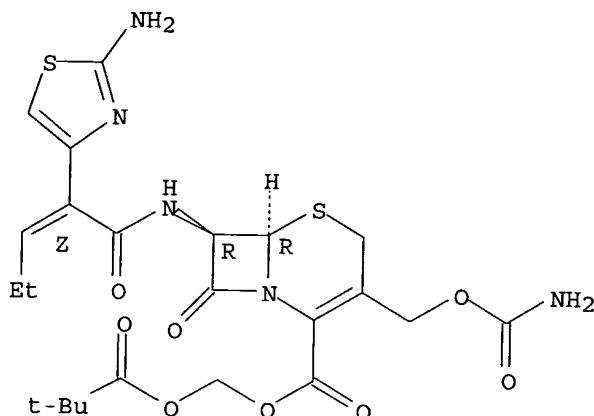
Double bond geometry as shown.



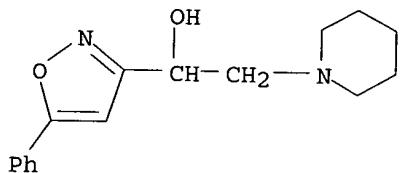
RN 105889-45-0 HCPLUS

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
3-[(aminocarbonyl)oxy]methyl]-7-[(2Z)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl]amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

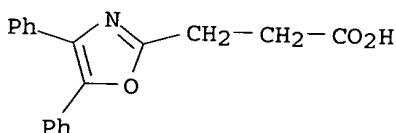
Absolute stereochemistry.
Double bond geometry as shown.



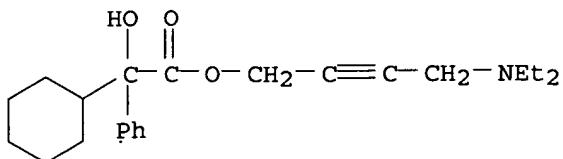
IT 2055-44-9, Perisoxal 21256-18-8, Oxaprozin
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (antiinflammatory; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)
 RN 2055-44-9 HCPLUS
 CN 1-Piperidineethanol, α -(5-phenyl-3-isoxazolyl)- (7CI, 8CI, 9CI) (CA INDEX NAME)



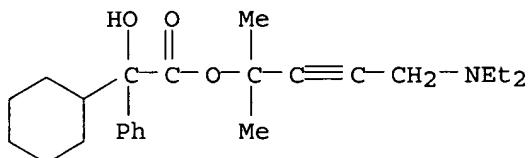
RN 21256-18-8 HCPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



IT 5633-20-5, Oxybutynin 129927-33-9, NS-21
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (bronchodilator; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)
 RN 5633-20-5 HCPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)

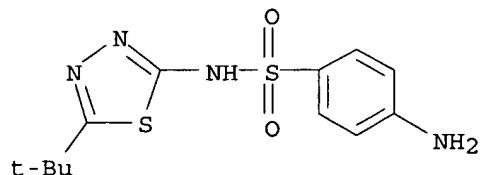


RN 129927-33-9 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, hydrochloride (9CI) (CA
 INDEX NAME)



● HCl

IT 535-65-9, Glybuthiazole
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (synthesis, activity and formulations of pharmaceutical
 compds. for treatment of oxidative stress and/or endothelial
 dysfunction)
 RN 535-65-9 HCAPLUS
 CN Benzenesulfonamide, 4-amino-N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]- (9CI) (CA INDEX NAME)



L61 ANSWER 43 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:742053 HCAPLUS
 DOCUMENT NUMBER: 133:310142
 TITLE: Synthesis, activity and formulations of pharmaceutical
 compounds for treatment of oxidative stress and/or
 endothelial dysfunction
 INVENTOR(S): Del Soldato, Piero
 PATENT ASSIGNEE(S): Nicox S.A., Fr.
 SOURCE: PCT Int. Appl., 159 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061537	A2	20001019	WO 2000-EP3234	20000411 <--
WO 2000061537	A3	20010927		
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RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
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EP 1169294	A2	20020109	EP 2000-925203	20000411 <--
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NZ 514267	A	20040625	NZ 2000-514267	20000411
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AU 778989	B2	20041223	AU 2000-44001	20000411
ZA 2001008127	A	20030103	ZA 2001-8127	20011003 <--
NO 2001004927	A	20011213	NO 2001-4927	20011010 <--
US 6869974	B1	20050322	US 2001-926326	20011015
US 2005261242	A1	20051124	US 2004-24857	20041230
PRIORITY APPLN. INFO.:			IT 1999-MI753	A 19990413
			WO 2000-EP3234	W 20000411
			US 2001-926326	A3 20011015

OTHER SOURCE(S) : MARPAT 133:310142

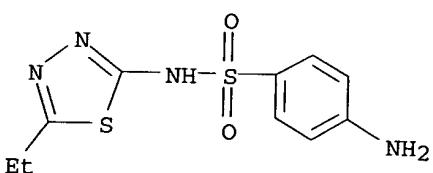
AB Compds. A-B-C-N(O)s and A-C1[N(O)s]-B1 or their salts [s is an integer 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacol. tests reported in the description; C and C1 are two bivalent radicals; the precursors of the radicals B and B1 are such as to meet the pharmacol. test reported in the description] were prepared for use as pharmaceuticals. Thus, (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalenylacetyl)cysteine 4-nitroxybutyl ester was prepared (NCX 2101) from naproxene and N-acetylcysteine in the first of 28 synthetic examples given. Pharmacol. test examples and tabular data are also given.

IT 94-19-9, Sulfaethidole 2055-44-9, Perisoxal 5633-20-5, Oxybutynin 21256-18-8, Oxaprozin 97519-39-6, Ceftibuten 105889-45-0, Cefcapene pivoxil 129927-33-9, NS21 135889-00-8, Cefcapene

RL: RCT (Reactant); RACT (Reactant or reagent)
(drug precursor)

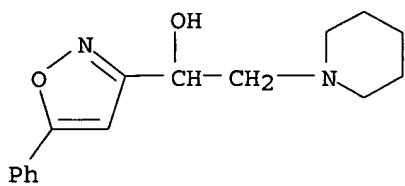
RN 94-19-9 HCPLUS

CN Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (9CI) (CA INDEX NAME)

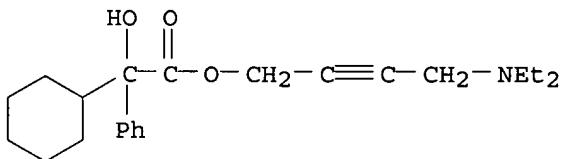


RN 2055-44-9 HCPLUS

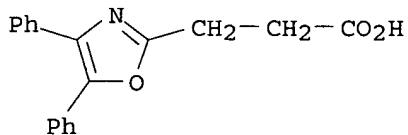
CN 1-Piperidineethanol, α -(5-phenyl-3-isoxazolyl)- (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)

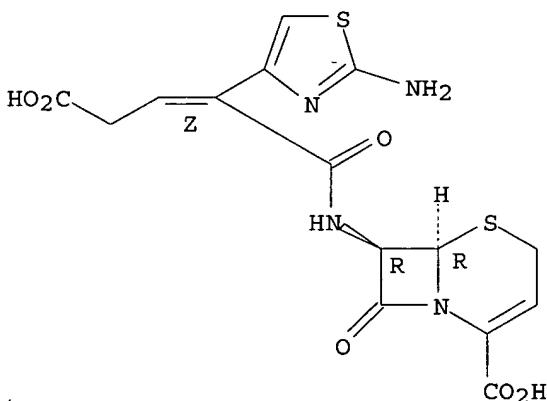


RN 21256-18-8 HCAPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 97519-39-6 HCAPLUS
 CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 7-[[[(2Z)-2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-,
 (6R,7R)- (9CI) (CA INDEX NAME)

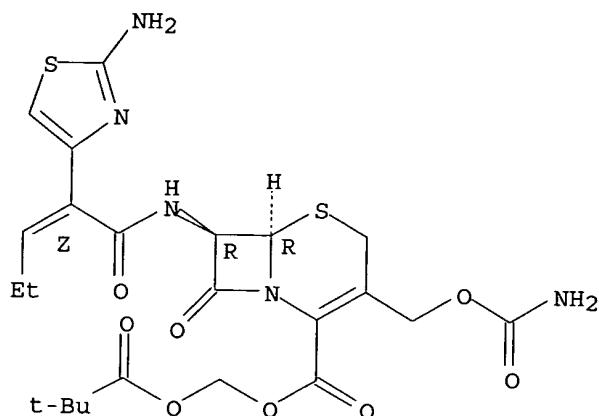
Absolute stereochemistry.
 Double bond geometry as shown.



RN 105889-45-0 HCAPLUS

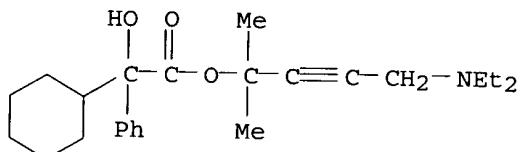
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 3-[(aminocarbonyl)oxy]methyl]-7-[(2Z)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl]amino]-8-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, (6R,7R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



RN 129927-33-9 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-1,1-dimethyl-2-butynyl ester, hydrochloride (9CI) (CA INDEX NAME)

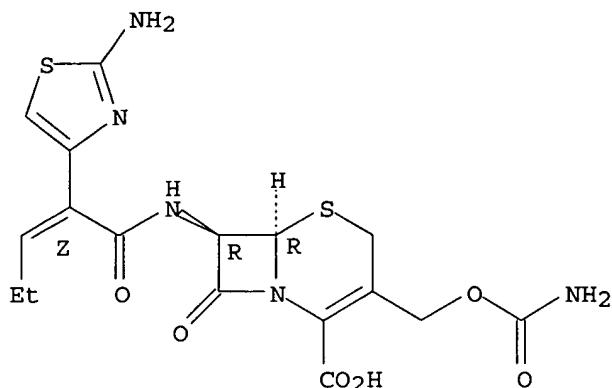


● HCl

RN 135889-00-8 HCPLUS

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
 3-[(aminocarbonyl)oxy]methyl]-7-[(2Z)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl]amino]-8-oxo-, (6R,7R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



L61 ANSWER 44 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:725436 HCAPLUS

DOCUMENT NUMBER: 133:301171

TITLE: Compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents

INVENTOR(S): Chen, Feng-jing; Patel, Manesh V.

PATENT ASSIGNEE(S): Lipocene, Inc., USA

SOURCE: PCT Int. Appl., 99 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059475	A1	20001012	WO 2000-US7342	20000316 <<
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6383471	B1	20020507	US 1999-287043	19990406 <<
CA 2366702	AA	20001012	CA 2000-2366702	20000316 <<
EP 1165048	A1	20020102	EP 2000-916547	20000316 <<
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			US 1999-287043	A 19990406
			WO 2000-US7342	W 20000316

AB The present invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of preparing such compns. by providing a composition of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compns. of the invention are particularly suitable for use in oral

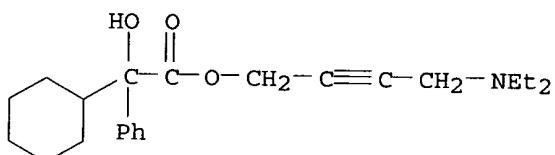
dosage forms. A carrier containing concentrated phosphoric acid 0.025, Tween-20

0.3, Arlacel 186 0.2, sodium taurocholate 0.15, propylene glycol 0.3 g was formulated. Itraconazole was included in the carrier at 30 mg/mL for testing the stability of the itraconazole solution upon dilution in simulated gastric fluid.

IT 5633-20-5, Oxybutynin 19216-56-9,
 Prazosin 21256-18-8, Oxaprozin 63590-64-7,
 Terazosin 74191-85-8, Doxazosin
 106133-20-4, Tamsulosin 124937-51-5,
 Tolterodine 139264-17-8, Zolmitriptan
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmaceutical compns. containing hydrophobic
 therapeutic agents and carriers containing ionizing agents and
 surfactants and triglycerides)

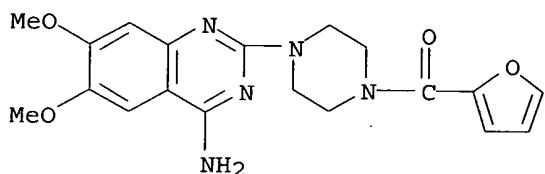
RN 5633-20-5 HCPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



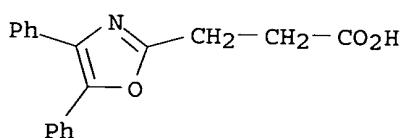
RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



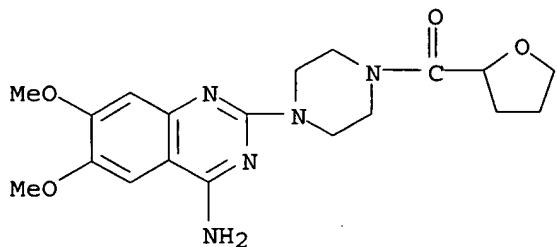
RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



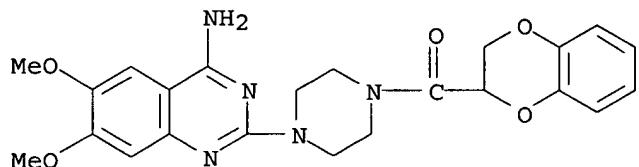
RN 63590-64-7 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS

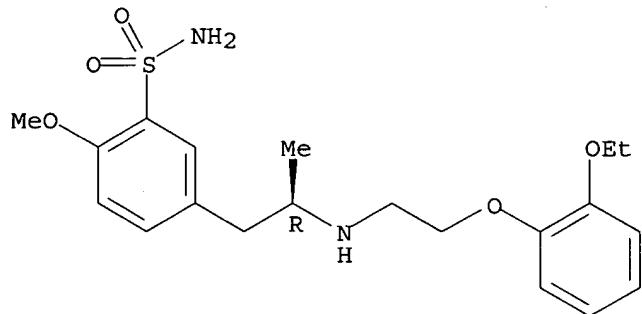
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[(2-(2-ethoxyphenoxy)ethyl)amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

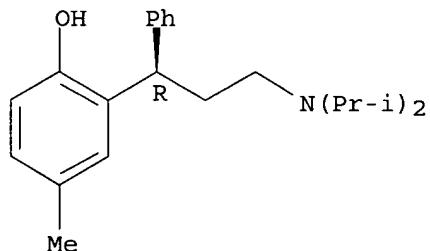
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCAPLUS

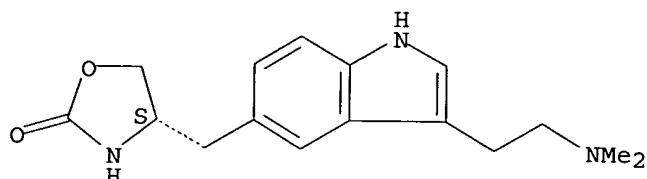
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



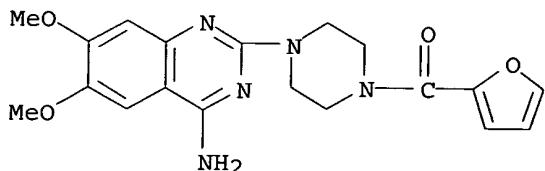
RN 139264-17-8 HCAPLUS
 CN 2-Oxazolidinone, 4-[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl-,
 (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

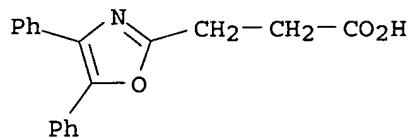


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

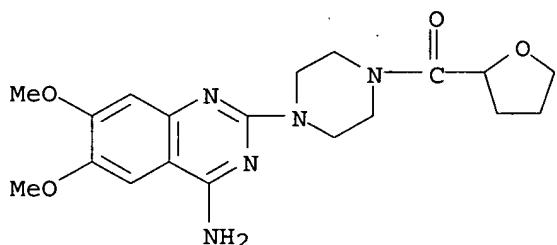
L61 ANSWER 45 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:720729 HCAPLUS
 DOCUMENT NUMBER: 136:256719
 TITLE: QSAR model for drug human oral bioavailability.
 [Erratum to document cited in CA133:159633]
 AUTHOR(S): Yoshida, Fumitaka; Topliss, John G.
 CORPORATE SOURCE: Division of Medicinal Chemistry College of Pharmacy,
 University of Michigan, Ann Arbor, MI, 48109-1065, USA
 SOURCE: Journal of Medicinal Chemistry (2000),
 43(24), 4723
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB On page 2578, Table 5, the correct footnote e is as follows: "e Weighting
 is 0.5, where the carbon α to the carbonyl is tertiary, or the
 carbonyl is attached to a ring with ortho substituents on each side, or
 the carbonyl can undergo intramol. hydrogen bonding with a nearby group.". On page 2580, in Table 6, under the "structural descriptors" column, the correct data for entries 96 and 133 is 7, 13 for both compds. Under the "drug" column, the correct spelling of the names for entries 83 and 107 are propranolol and chlorthalidone, resp.
 IT 19216-56-9, Prazosin 21256-18-8, Oxaprozin
 63590-64-7, Terazosin 74191-85-8,
 Doxazosin
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP
 (Properties); BIOL (Biological study)
 (QSAR model for drug human oral bioavailability (Erratum))
 RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



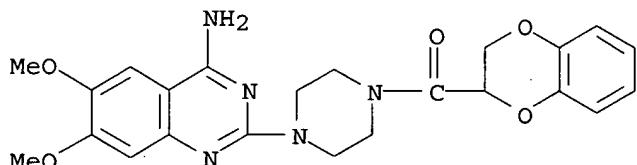
RN 21256-18-8 HCPLUS
 CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 46 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:720700 HCPLUS
 DOCUMENT NUMBER: 134:25113
 TITLE: Classification of multidrug-resistance reversal agents using structure-based descriptors and linear discriminant analysis
 AUTHOR(S): Bakken, Gregory A.; Jurs, Peter C.
 CORPORATE SOURCE: Department of Chemistry, The Pennsylvania State University, University Park, PA, 16802, USA
 SOURCE: Journal of Medicinal Chemistry (2000), 43(23), 4534-4541
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Linear discriminant anal. is used to generate models to classify multidrug-resistance reversal agents based on activity. Models are generated and evaluated using multidrug-resistance reversal activity values for 609 compds. measured using adriamycin-resistant P388 murine

leukemia cells. Structure-based descriptors numerically encode mol. features which are used in model formation. Two types of models are generated: one type to classify compds. as inactive, moderately active, and active (three-class problem) and one type to classify compds. as inactive or active without considering the moderately active class (two-class problem). Two activity distributions are considered, where the separation between inactive and active compds. is different. When the separation

between inactive and active classes is small, a model based on nine topol. descriptors is developed that produces a classification rate of 83.1% correct for an external prediction set. Larger separation between active and inactive classes raises the prediction set classification rate to 92.0% correct using a model with six topol. descriptors. Models are further validated through Monte Carlo expts. in which models are generated after class labels have been scrambled. The classification rates achieved demonstrate that the models developed could serve as a screening mechanism to identify potentially useful multidrug-resistance reversal (MDRR) agents from large libraries of compds.

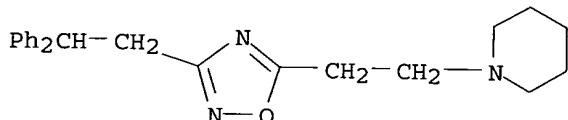
IT 982-43-4, Prenoxdiazine 5633-20-5, Oxybutynin
5696-09-3, Proxazole 66969-81-1, Tiodazosin

74191-85-8, Doxazosin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(classification of multidrug-resistance reversal agents using structure-based descriptors and linear discriminant anal. in relation to drug screening)

RN 982-43-4 HCPLUS

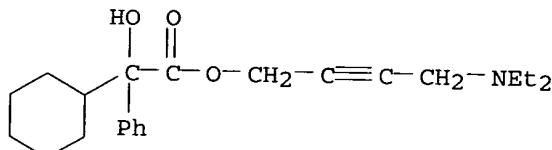
CN Piperidine, 1-[2-[3-(2,2-diphenylethyl)-1,2,4-oxadiazol-5-yl]ethyl]-, monohydrochloride (8CI, 9CI) (CA INDEX NAME)



● HCl

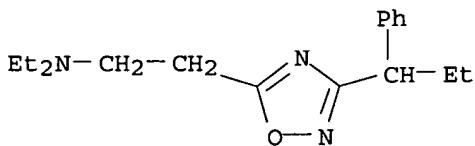
RN 5633-20-5 HCPLUS

CN Benzeneacetic acid, α-cyclohexyl-α-hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)

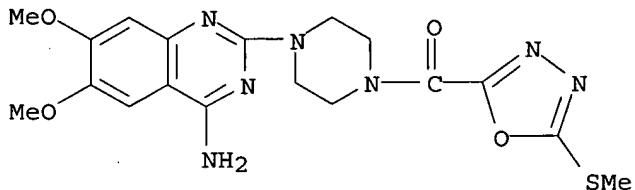


RN 5696-09-3 HCPLUS

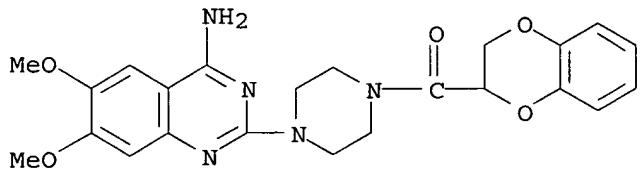
CN 1,2,4-Oxadiazole-5-ethanamine, N,N-diethyl-3-(1-phenylpropyl)- (9CI) (CA INDEX NAME)



RN 66969-81-1 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 47 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:608551 HCAPLUS
 DOCUMENT NUMBER: 133:213151
 TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
 INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
 PATENT ASSIGNEE(S): Lipocene, Inc., USA
 SOURCE: PCT Int. Appl., 98 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 13
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 6294192 B1 20010925 US 1999-258654 19990226 <--
CA 2365536 AA 20000831 CA 2000-2365536 20000105 <--
AU 2000022242 A5 20000914 AU 2000-22242 20000105 <--
AU 771659 B2 20040401
EP 1158959 A1 20011205 EP 2000-901394 20000105 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO
JP 2002537317 T2 20021105 JP 2000-600619 20000105 <--
NZ 513810 A 20040227 NZ 2000-513810 20000105
PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent.

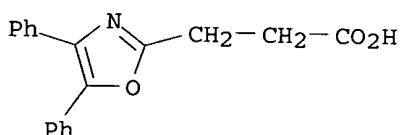
The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical composition contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.

IT 21256-18-8, Oxaprozin 63590-64-7, Terazosin
106133-20-4, Tamsulosin 139264-17-8,
Zolmitriptan

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of
hydrophobic therapeutic agents)

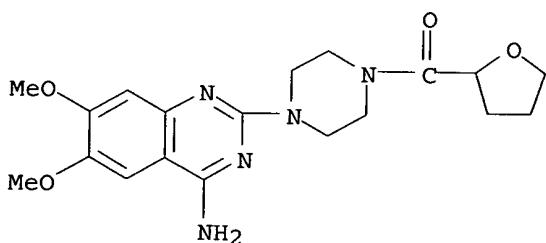
RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCPLUS

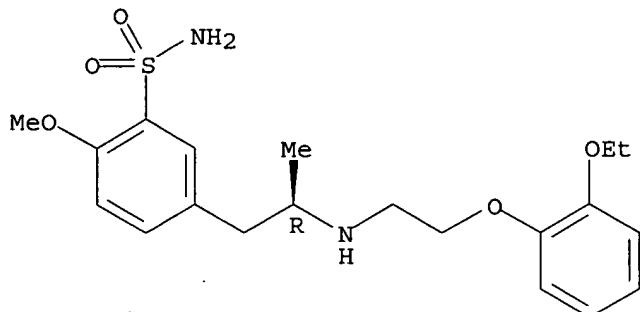
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

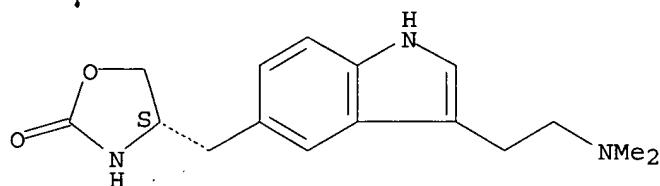
Absolute stereochemistry. Rotation (-).



RN 139264-17-8 HCPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 48 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:375684 HCPLUS

DOCUMENT NUMBER: 133:159633

TITLE: QSAR Model for Drug Human Oral Bioavailability

AUTHOR(S): Yoshida, Fumitaka; Topliss, John G.

CORPORATE SOURCE: Division of Medicinal Chemistry College of Pharmacy, University of Michigan, Ann Arbor, MI, 48109-1065, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(13), 2575-2585

PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: American Chemical Society

LANGUAGE: English

AB The quant. structure-bioavailability relationship of 232 structurally diverse drugs was studied to evaluate the feasibility of constructing a predictive model for the human oral bioavailability of prospective new medicinal agents. The oral bioavailability determined in human adults was assigned one of four ratings and analyzed in relation to physicochem. and structural factors by the ORMUCS (ordered multicategorical classification method using the simplex technique) method. A systematic examination of various physicochem. parameters relating primarily to absorption, and structural elements which could influence metabolism, was carried out to analyze their effects on the bioavailability classification of drugs in the data set. Lipophilicity, expressed as the distribution coefficient at pH

6.5, was found to be a significant factor influencing bioavailability. The observation that acids generally had better bioavailability characteristics than bases, with neutral compds. between, led to the formulation of a new parameter, $\Delta \log D$ ($\log D_{6.5} - \log D_{7.4}$), which proved to be an important contributor in improving the classification results. The addition of 15 structural descriptors relating primarily to well-known metabolic processes yielded a satisfactory QSAR equation which had a correct classification rate of 71% (97% within one class) and a Spearman rank correlation coefficient (R_s) of 0.851, despite the diversity of structure and pharmacol. activity in the compound set. In leave-one-out tests, an average of 67% of drugs were correctly classified (96% within one class) with an R_s of 0.812. The relationship formulated identified significant factors influencing bioavailability and assigned them quant. values expressing their contribution. The predictive power of the model was evaluated using a sep. test set of 40 compds., of which 60% (95% within one class) were correctly classified. Since the necessary physicochem. parameters can be calculated or estimated and the structural descriptors are obtained from an inspection of the structure, the model enables a rough estimate to be made of the prospective human oral bioavailability of unsynthesized compds. Also, the model has the advantage of transparency in that it indicates which factors may affect bioavailability and the extent of that effect. This could be useful in designing compds. which are more bioavailable. Refinement of the model is possible as more bioavailability data becomes available. Potential uses are in drug design, prioritization of compds. for synthesis, and selection for detailed studies of early compound leads in drug discovery programs.

IT 19216-56-9, Prazosin 21256-18-8, Oxaprozin
63590-64-7, Terazosin 74191-85-8,

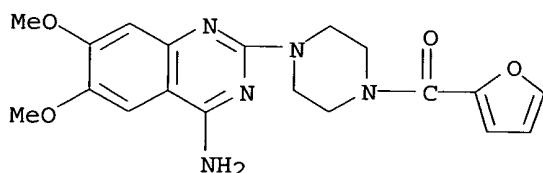
Doxazosin

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(QSAR model for drug human oral bioavailability)

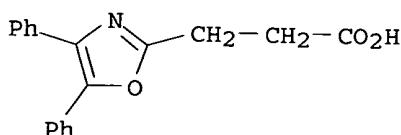
RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



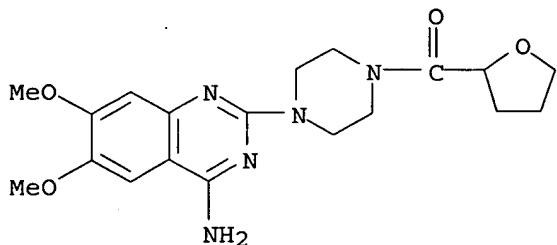
RN 21256-18-8 HCPLUS

CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)

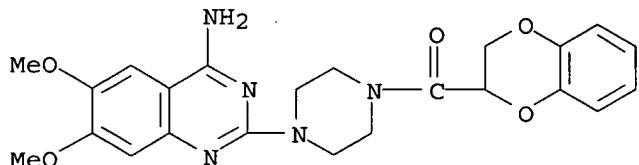


RN 63590-64-7 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

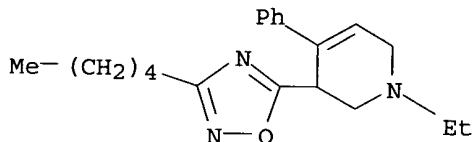
L61 ANSWER 49 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:59414 HCAPLUS
 DOCUMENT NUMBER: 130:223152
 TITLE: Identification and Characterization of m1 Selective Muscarinic Receptor Antagonists
 AUTHOR(S): Augelli-Szafran, Corinne E.; Blankley, C. John; Jaen, Juan C.; Moreland, David W.; Nelson, Carrie B.; Penvose-Yi, Jan R.; Schwarz, Roy D.; Thomas, Anthony J.
 CORPORATE SOURCE: Department of Medicinal Chemistry Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI, 48105, USA
 SOURCE: Journal of Medicinal Chemistry (1999), 42(3), 356-363
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A series of esters of 1,4-disubstituted tetrahydropyridinecarboxylic acids has been synthesized and characterized as potential m1 selective muscarinic receptor antagonists. The affinity of these compds. for the five human muscarinic receptor subtypes (Hm1-Hm5) was determined by the displacement of [3H]-NMS binding using membranes from transfected Chinese hamster ovarian cells. One of the most potent and selective compds. of this series is hexyl 1-ethyl-4-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate which has an IC50 value of 27.3 nM at the m1 receptor and possesses 100-fold (m2), 48-fold (m3), 74-fold (m4), and 19-fold (m5) selectivities at the other receptors. Thus, this analog appears to be more selective on the basis of binding than the prototypical m1 antagonist, pirenzepine. Functional data, such as the inhibition of carbachol-stimulated phosphatidylinositol hydrolysis, on selected analogs

confirmed the muscarinic antagonistic properties of this chemical series.
 IT 221162-13-6P 221162-16-9P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of phenyltetrahydropyridinecarboxylates with selective m₁ antimuscarinic activity)
 RN 221162-13-6 HCAPLUS
 CN Pyridine, 1-ethyl-1,2,3,6-tetrahydro-3-(3-pentyl-1,2,4-oxadiazol-5-yl)-4-phenyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 221162-07-8

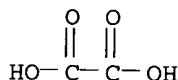
CMF C20 H27 N3 O



CM 2

CRN 144-62-7

CMF C2 H2 O4



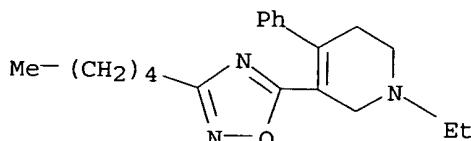
RN 221162-16-9 HCAPLUS

CN Pyridine, 1-ethyl-1,2,3,6-tetrahydro-5-(3-pentyl-1,2,4-oxadiazol-5-yl)-4-phenyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 221162-09-0

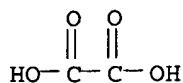
CMF C20 H27 N3 O



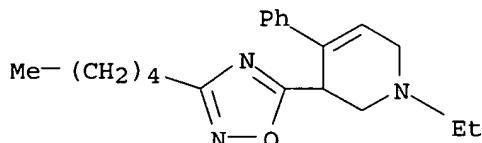
CM 2

CRN 144-62-7

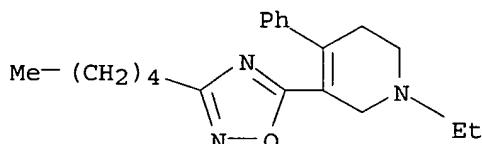
CMF C2 H2 O4



IT 221162-07-8P 221162-09-0P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of phenyltetrahydropyridinecarboxylates with selective m1
 antimuscarinic activity)
 RN 221162-07-8 HCPLUS
 CN Pyridine, 1-ethyl-1,2,3,6-tetrahydro-3-(3-pentyl-1,2,4-oxadiazol-5-yl)-4-phenyl- (9CI) (CA INDEX NAME)

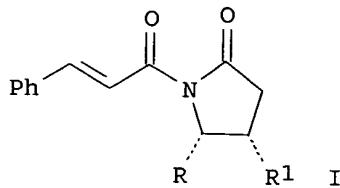


RN 221162-09-0 HCPLUS
 CN Pyridine, 1-ethyl-1,2,3,6-tetrahydro-5-(3-pentyl-1,2,4-oxadiazol-5-yl)-4-phenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 50 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1998:659150 HCPLUS
 DOCUMENT NUMBER: 130:13809
 TITLE: Asymmetric Total Synthesis of (+)-Tolterodine, a New Muscarinic Receptor Antagonist, via Copper-Assisted Asymmetric Conjugate Addition of Aryl Grignard Reagents to 3-Phenyl-prop-2-enoyloxazolidinones
 AUTHOR(S): Andersson, Pher G.; Schink, Hans E.; Oesterlund, Krister
 CORPORATE SOURCE: Department of Organic Chemistry, University of Uppsala, Uppsala, S-751 21, Swed.
 SOURCE: Journal of Organic Chemistry (1998), 63(22), 8067-8070
 CODEN: JOCEAH; ISSN: 0022-3263
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB Grignard reaction of the cinnamoyloxazolidinones I [R = (R)-CHMe₂, R1 = H, (R)-CHMe₂] with 5,2-Me(MeO)C₆H₃MgBr gave (S)-5,2-Me(MeO)C₆H₃CHPhCH₂CO₂H. Similar reaction of I [R = (S)-Me, (S)-Ph, R1 = (S)-Ph; R = (S)-Ph, R1 = H] gave (R)-5,2-Me(MeO)C₆H₃CHPhCH₂CO₂H. I [R, R1 = (S)-Ph] was used to prepare (+)-tolterodine.

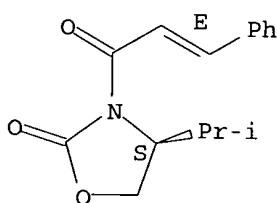
IT 112459-60-6

RL: RCT (Reactant); RACT (Reactant or reagent)
 (asym. total synthesis of (+)-tolterodine via copper-assisted
 asym. conjugate addition of aryl Grignard reagents to 3-phenyl-prop-2-
 enoyloxazolidinones)

RN 112459-60-6 HCPLUS

CN 2-Oxazolidinone, 4-(1-methylethyl)-3-[(2E)-1-oxo-3-phenyl-2-propenyl]-,
 (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
 Double bond geometry as shown.



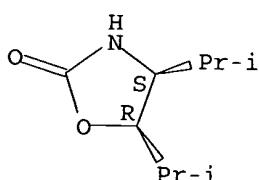
IT 215929-24-1P 215929-25-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (asym. total synthesis of (+)-tolterodine via copper-assisted
 asym. conjugate addition of aryl Grignard reagents to 3-phenyl-prop-2-
 enoyloxazolidinones)

RN 215929-24-1 HCPLUS

CN 2-Oxazolidinone, 4,5-bis(1-methylethyl)-, (4S,5R)- (9CI) (CA INDEX NAME)

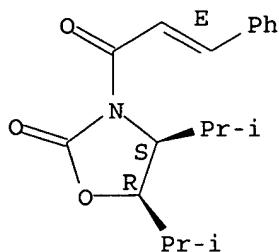
Absolute stereochemistry. Rotation (-).



RN 215929-25-2 HCPLUS

CN 2-Oxazolidinone, 4,5-bis(1-methylethyl)-3-[(2E)-1-oxo-3-phenyl-2-propenyl]-,
 (4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 51 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:198232 HCPLUS

DOCUMENT NUMBER: 128:204905

TITLE: Process for the manufacture of intermediates for the preparation of doxazosin, terazosin, prazosin, tiiodazosin and related antihypertensive medicines

INVENTOR(S): Zhou, Tianhao; Weeratunga, Gamin; Murthy, K. S. Keshava; Guntoori, Bhaskar Reddy

PATENT ASSIGNEE(S): Acic (Canada) Inc., Can.

SOURCE: Can. Pat. Appl., 18 pp.

CODEN: CPXXEB

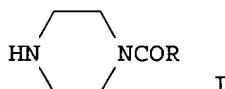
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2173408	AA	19971004	CA 1996-2173408	19960403 <-
CA 2173408	C	20010904		
US 5919931	A	19990706	US 1996-627454 CA 1996-2173408	19960404 <- A 19960403
PRIORITY APPLN. INFO.:				
OTHER SOURCE(S):	CASREACT 128:204905; MARPAT 128:204905			
GI				



AB Mono-acylated piperazines I (R = tetrahydro-2-furyl, 2-furyl, etc.), intermediates for preparation of doxazosin, terazosin, prazosin, and tiiodazosin, were prepared by direct amidation of RCO2R1 (same R; R1 = H, Me, Et, lower alkyl) with piperazine. E.g., to a suspension of piperazine in xylenes was added Me 2-furoate. The yield of N-2-furoylpiperazine was 64%.

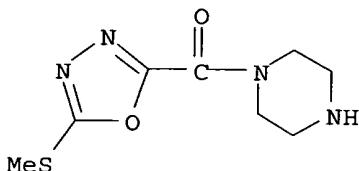
IT 73775-99-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(manufacture of intermediates for the preparation of doxazosin,
terazosin, prazosin, tiotiazosin and related
antihypertensive medicines)

RN 73775-99-2 HCAPLUS

CN Piperazine, 1-[[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]- (9CI) (CA INDEX NAME)

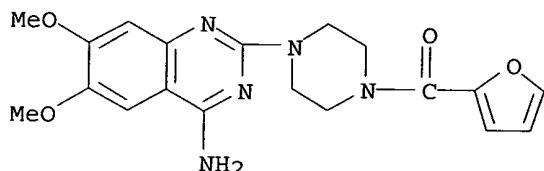


IT 19216-56-9P, Prazosin 63590-64-7P,
Terazosin 66969-81-1P, Tiotiazosin 74191-85-8P,
Doxazosin

RL: PNU (Preparation, unclassified); PREP (Preparation)
(manufacture of intermediates for the preparation of doxazosin,
terazosin, prazosin, tiotiazosin and related
antihypertensive medicines)

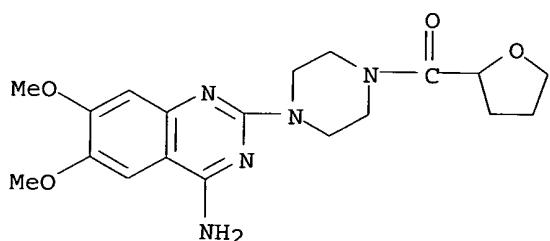
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



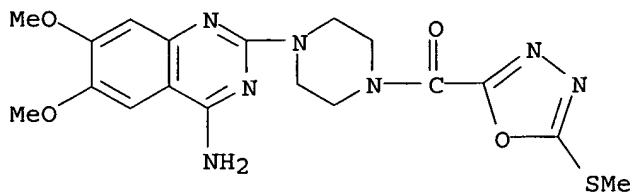
RN 63590-64-7 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



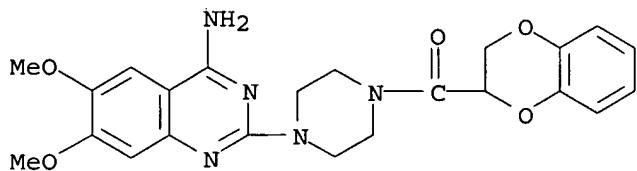
RN 66969-81-1 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 52 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:367536 HCAPLUS

DOCUMENT NUMBER: 127:60207

TITLE: Carcinogenicity testing and the evaluation of regulatory requirements for pharmaceuticals

AUTHOR(S): Contrera, Joseph F.; Jacobs, Abigail C.; DeGeorge, Joseph J.

CORPORATE SOURCE: Office Testing and Research and Office of Review Management, U.S. Food and Drug Admin., Center for Drug Evaluation and Research, Rockville, MD, 20857, USA

SOURCE: Regulatory Toxicology and Pharmacology (1997), 25(2), 130-145

CODEN: RTOPDW; ISSN: 0273-2300

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

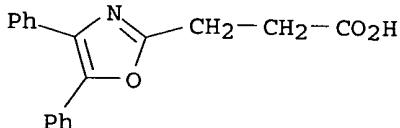
AB Database The results of rat and mouse carcinogenicity studies for 282 human pharmaceuticals in the FDA database were analyzed and compared as part of an International Conference on Harmonization (ICH) evaluation of rodent carcinogenicity studies and their utility for carcinogenicity testing. A majority of the carcinogenicity studies in the FDA database were carried out in Sprague-Dawley-derived rats and Swiss-Webster-derived CD-1 mice in contrast to Fisher 344 rats and B6C3F1 mice employed in National Toxicol. Program (NTP) studies. Despite the differences in rodent strains, the relative proportion of compds. with pos. findings (44.3%) and the degree of overall concordance between rats and mice (74.1%) in the FDA database were similar to the NTP rodent carcinogenicity database. Carcinogenicity studies in two rodent species are necessary primarily to identify trans-species tumorigens, which are considered to pose a relatively greater potential risk to humans than single species pos. compds. Two-year carcinogenicity studies in both rats and mice may not be the only means of identifying transspecies tumorigens. Sufficient experience is now available for some alternative in vivo carcinogenicity models to support their application as complementary studies in combination with a single 2-yr carcinogenicity study to identify trans-species tumorigens. Our anal. of the rodent carcinogenicity studies

supports such an approach for assessing carcinogenic potential without compromising the public health.

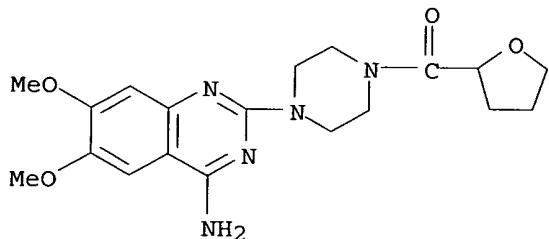
IT 21256-18-8, Oxaprozin 63590-64-7, Terazosin
 74191-85-8, Doxazosin
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (rat and mouse carcinogenicity studies and evaluation of regulatory requirements for pharmaceuticals)

RN 21256-18-8 HCAPLUS

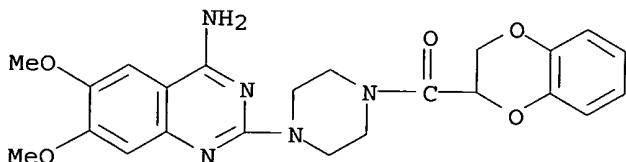
CN 2-Oxazolepropanoic acid, 4,5-diphenyl- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 53 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:296396 HCAPLUS

DOCUMENT NUMBER: 125:58368

TITLE: Conformationally restrained β -blocking oxime ethers. 4. Chiral 2-(3'-(5'-p-chlorophenyl)isoxazolidinyl)ethanolamines as conformationally restrained analogs of methyloxyiminomethyl (MOIM) β -adrenergic antagonists: synthesis, configuration and β -adrenergic properties

AUTHOR(S): Balsamo, A.; Breschi, M. C.; Chiellini, G.; Cozzini, P.; Domiano, P.; Macchia, M.; Manera, C.; Martinelli, A.; Nencetti, S.; et al.

CORPORATE SOURCE: Dip. Sci. Farm., Univ. Pisa, Pisa, 56126, Italy

SOURCE: European Journal of Medicinal Chemistry (1996), 31(4), 291-300

CODEN: EJMCA5; ISSN: 0223-5234

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The chiral N-isopropyl- and N-t-butyl-substituted 2-(3'-(5'-p-chlorophenyl)isoxazolidinyl)ethanolamines 2, 3, which can be viewed as conformationally restrained analogs of the corresponding methyloxyiminomethyl (MOIM) β -adrenergic antagonists 1, were synthesized from optically active precursors with a known absolute configuration. The structure and configuration of the intermediate and final products 2, 3 were assigned on the basis of a comparison of the H NMR spectral data of all compds., crystallog. anal. of one of the intermediates [(2R,5'S)-7] and knowledge of the configuration of the chiral starting compds. The compds. showing affinity indexes lower than 10 μ M on β 1-adrenoceptors were also assayed for their β -adrenergic activity by functional tests on isolated preps. The results showed that the cyclic derivs. 2, 3 possess a capacity to interact with β -receptors which is clearly lower than that of the corresponding MOIM analogs 1.

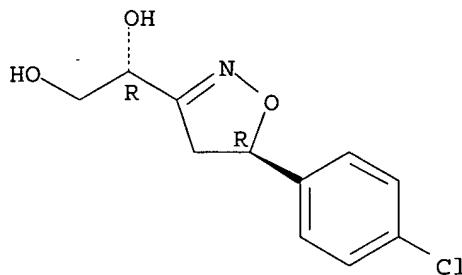
IT 177950-46-8P 177950-47-9P 178035-84-2P
178035-85-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of chiral chlorophenylisoxazolidinyl)ethanolamines as conformationally restrained analogs of methyloxyiminomethyl β -adrenergic antagonists)

RN 177950-46-8 HCPLUS

CN 1,2-Ethanediol, 1-[5-(4-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

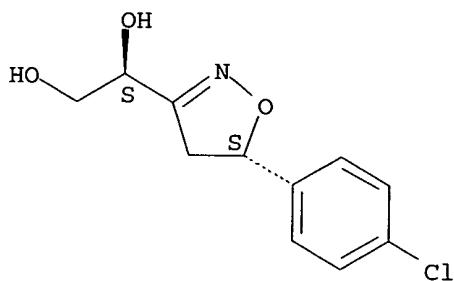
Absolute stereochemistry. Rotation (-).



RN 177950-47-9 HCPLUS

CN 1,2-Ethanediol, 1-[5-(4-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

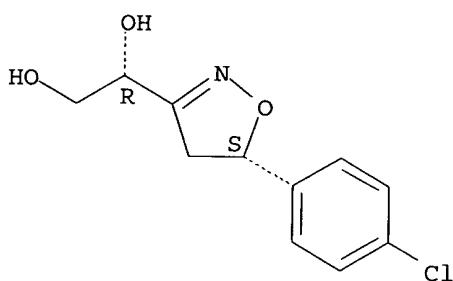
Absolute stereochemistry. Rotation (+).



RN 178035-84-2 HCAPLUS

CN 1,2-Ethanediol, 1-[5-(4-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

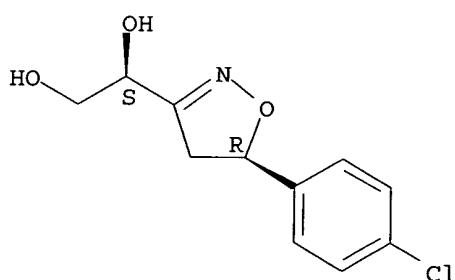
Absolute stereochemistry. Rotation (+).



RN 178035-85-3 HCAPLUS

CN 1,2-Ethanediol, 1-[5-(4-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 54 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:185164 HCAPLUS

DOCUMENT NUMBER: 124:277988

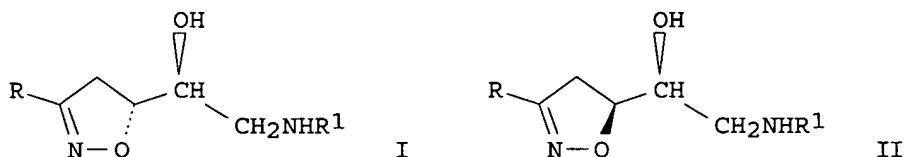
TITLE: Conformationally restrained β -blocking oxime ethers. 3. Synthesis and β -adrenergic antagonistic activity of diastereomeric anti and syn

AUTHOR(S): 2-(5'-(3'-methyl)isoxazolidinyl)-N-alkylethanolamines
Breschi, M. C.; Macchia, M.; Manera, C.; Micali, E.;
Nardini, E.; Nencetti, S.; Rossello, A.; Scatizzi, R.

CORPORATE SOURCE: Istituto Policattedra Discipline Biologiche,

SOURCE: Universita Pisa, Pisa, 56100, Italy
 European Journal of Medicinal Chemistry (1996), 31(2), 159-63
 CODEN: EJMCA5; ISSN: 0223-5234

PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The diastereomeric anti (I, R=Me, R1=i-Pr and I, R=Me, R1=tert-Bu) and syn (II, R1=i-Pr, R=Me and II, R1=tert-Bu, R=Me) 2-(5'-(3'-methyl)isoxazolidinyl)-N-alkylethanamines were synthesized and assayed for their β_1 - and β_2 -adrenergic antagonistic activity by functional tests on isolated preps. The pharmacol. results, which were compared with those previously obtained for the corresponding isoxazoline analogs substituted in the 3'-position with an iso-Pr group instead of the Me group in I, indicated that the β -adrenergic antagonistic activity of the 3'-alkyl-substituted compds. is not substantially influenced by the size of the alkyl substituent.

IT 147288-96-8 147289-02-9 147289-04-1

147289-06-3

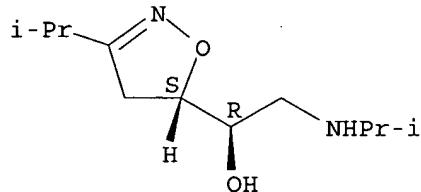
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synthesis and β - adrenergic antagonistic activity of diastereomeric anti and syn 2-(5'-(3'-methyl)isoxazolidinyl)-N-alkylethanamines)

RN 147288-96-8 HCPLUS

CN 5-Isoxazolemethanol, 4,5-dihydro-3-(1-methylethyl)- α -[(1-methylethyl)amino]methyl-, (R*,S*)- (9CI) (CA INDEX NAME)

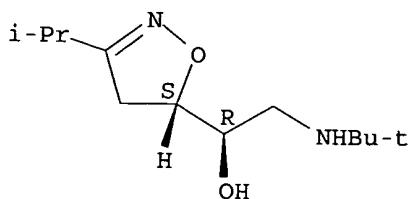
Relative stereochemistry.



RN 147289-02-9 HCPLUS

CN 5-Isoxazolemethanol, α -[(1,1-dimethylethyl)amino]methyl]-4,5-dihydro-3-(1-methylethyl)-, (R*,S*)- (9CI) (CA INDEX NAME)

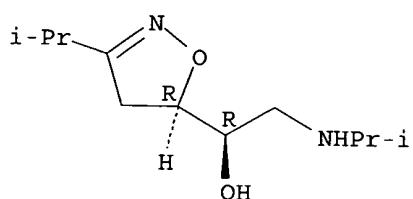
Relative stereochemistry.



RN 147289-04-1 HCAPLUS

CN 5-Isoxazolemethanol, 4,5-dihydro-3-(1-methylethyl)- α -[(1-methylethyl)amino]methyl-, (R*,R*)- (9CI) (CA INDEX NAME)

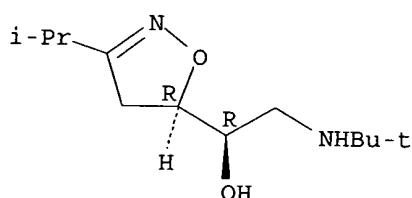
Relative stereochemistry.



RN 147289-06-3 HCAPLUS

CN 5-Isoxazolemethanol, α -[(1,1-dimethylethyl)amino]methyl]-4,5-dihydro-3-(1-methylethyl)-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L61 ANSWER 55 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:73869 HCAPLUS

DOCUMENT NUMBER: 124:194726

TITLE: (2S,4S)-2-Amino-4-(4,4-diphenylbut-1-yl)-pentane-1,5-dioic Acid: A Potent and Selective Antagonist for Metabotropic Glutamate Receptors Negatively Linked to Adenylate Cyclase

AUTHOR(S): Wermuth, Camille G.; Mann, Andre; Schoenfelder, Angele; Wright, Rebecca A.; Johnson, Bryan G.; Burnett, J. Paul; Mayne, Nancy G.; Schoepp, Darryle D.

CORPORATE SOURCE: Centre de Neurochimie, CNRS, Strasbourg, Fr.
SOURCE: Journal of Medicinal Chemistry (1996), 39(4), 814-16PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623
American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 124:194726

AB 2S,4S-2-Amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid is a

structurally novel antagonist for cAMP coupled metabotropic glutamate receptors (mGluRs). This compound selectively displaced metabotropic glutamate receptor binding and reversed glutamate agonist-induced inhibition of forskolin-stimulated cAMP formation in human mGluR2 expressing cells at low μ M concns. 2S,4S-2-Amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid had no appreciable affinity at ionotropic glutamate receptors or functional activities in cells expressing human mGluR1 α or mGluR5 receptors. 2S,4S-2-Amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid represents a new analog of glutamate to investigate antagonism of cAMP-coupled mGluRs.

IT 169756-48-3P 169872-36-0P 174319-37-0P

174393-14-7P

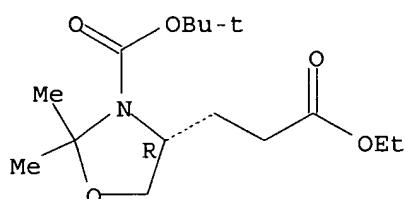
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; prepn of a diphenylbutyl glutamate deriv as a selective antagonist for metabotropic glutamate receptors neg. linked to adenylate cyclase)

RN 169756-48-3 HCPLUS

CN 4-Oxazolidinepropanoic acid, 3-[(1,1-dimethylethoxy)carbonyl]-2,2-dimethyl-, ethyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

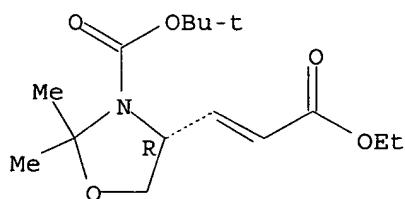


RN 169872-36-0 HCPLUS

CN 3-Oxazolidinecarboxylic acid, 4-(3-ethoxy-3-oxo-1-propenyl)-2,2-dimethyl-, 1,1-dimethylethyl ester, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

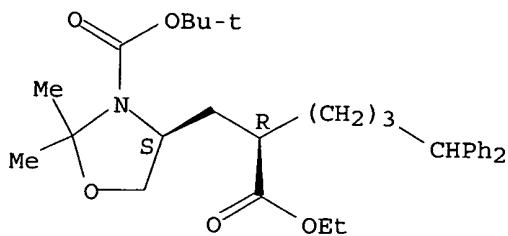
Double bond geometry unknown.



RN 174319-37-0 HCPLUS

CN 4-Oxazolidinepropanoic acid, 3-[(1,1-dimethylethoxy)carbonyl]- α -(4,4-diphenylbutyl)-2,2-dimethyl-, ethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

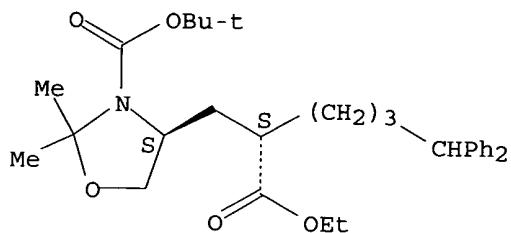
Absolute stereochemistry.



RN 174393-14-7 HCPLUS

CN 4-Oxazolidinepropanoic acid, 3-[(1,1-dimethylethoxy)carbonyl]-α-(4,4-diphenylbutyl)-2,2-dimethyl-, ethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L61 ANSWER 56 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:856174 HCPLUS

DOCUMENT NUMBER: 123:246794

TITLE: Method for preventing or reducing photosensitivity and/or phototoxicity reactions to medications

INVENTOR(S): Klimstra, Paul Dale; Roniker, Barbara; Swabb, Edward Allen

PATENT ASSIGNEE(S): G. D. Searle and Co., USA

SOURCE: PCT Int. Appl., 137 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

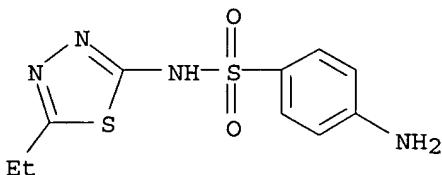
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

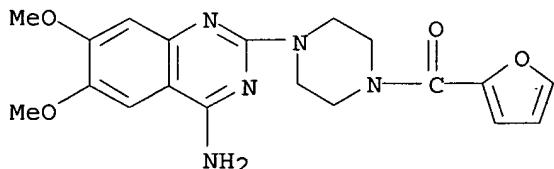
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9520387	A1	19950803	WO 1995-US213	19950112 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5668134	A	19970916	US 1994-188296	19940128 <--
AU 9515605	A1	19950815	AU 1995-15605	19950112 <--
EP 741570	A1	19961113	EP 1995-907337	19950112 <--
EP 741570	B1	20030507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 239478	E	20030515	AT 1995-907337	19950112 <--

PT 741570	T 20030930	PT 1995-907337	19950112 <--
EP 1384479	A1 20040128	EP 2003-9533	19950112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE			
ES 2199238	T3 20040216	ES 1995-907337	19950112
US 6172069	B1 20010109	US 1997-936572	19970924 <--
PRIORITY APPLN. INFO.:		US 1994-188296	A1 19940128
		EP 1995-907337	A3 19950112
		WO 1995-US213	W 19950112
		US 1995-438002	B1 19950509

- AB A method for preventing or reducing a photosensitivity and/or phototoxicity reaction which may be caused by a once-per-day dose of a medication comprises administering the prescribed or suggested dose of the medication to the patient during the evening or early morning hours. The present invention also provides a method for treating an infection in a patient in a manner which prevents or reduces a photosensitivity and/or phototoxicity reaction which method comprises orally administering to the patient a once-a-day dose of 25-700 mg of lomefloxacin HCl during the evening or early morning hours. The present invention also provides an article of manufacture comprising: (1) a packaging material, and (2) a once-a-day medication which causes a photosensitivity and/or a phototoxicity reaction in a patient contained within said packaging material and wherein said packaging material comprises a label which indicates that such a reaction is prevented or reduced by administering the medication to the patient during the evening or early morning hours.
- IT 94-19-9, Sulfaethidole 19216-56-9, Prazosin
 RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (method for preventing or reducing photosensitivity and/or phototoxicity reactions to drugs in humans)
- RN 94-19-9 HCPLUS
- CN Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (9CI) (CA INDEX NAME)



- RN 19216-56-9 HCPLUS
- CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)

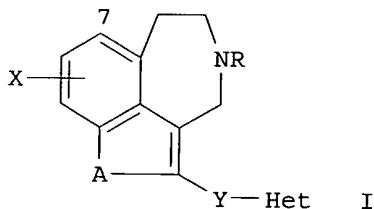


L61 ANSWER 57 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:526601 HCPLUS
 DOCUMENT NUMBER: 122:265353
 TITLE: Tetrahydrothieno- or tetrahydrofuro[4,3,2-

ef] [3]benzazepine derivatives useful as
 α -adrenergic receptor antagonists
INVENTOR(S) : Bondinell, William Edward; Demarinis, Robert Michael;
Ku, Thomas Wen-fu; Pfeiffer, Francis Richard; Shah,
Dinubhai Himatlal; Venslavsky, Joseph Walter
PATENT ASSIGNEE(S) : Smithkline Beecham Corp., USA
SOURCE: PCT Int. Appl., 42 pp.
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9419354	A1	19940901	WO 1994-US1739	19940216 <--
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9401027	A	19941111	ZA 1994-1027	19940215 <--
CA 2156186	AA	19940901	CA 1994-2156186	19940216 <--
AU 9462433	A1	19940914	AU 1994-62433	19940216 <--
EP 684949	A1	19951206	EP 1994-909685	19940216 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08507069	T2	19960730	JP 1994-519148	19940216 <--
US 5599810	A	19970204	US 1995-505297	19951020 <--
PRIORITY APPLN. INFO.:			US 1993-17713	A 19930216
			WO 1994-US1739	W 19940216

OTHER SOURCE(S) : MARPAT 122:265353
GI



AB α -Adrenergic receptor antagonists I [X = H, halo, CF₃, alkyl, COR₁, CO₂R₂, CONR₂R₂, cyano, NO₂, NR₂R₃, OR₃, alkylthio, S(CH₂)₀₋₆Ph, SCF₃, or combinations (\leq 3 groups); R = H, alkyl, alkenyl; R₁ = alkyl, (CH₂)₀₋₆Ph; R₂ = H, alkyl, (CH₂)₀₋₆Ph; R₃ = groups given for R₂, COR₁, SO₂R₁; A = O, S; Y = bond, (CH₂)₁₋₄, CH:, CH:CHQ, (CH₂)₀₋₂E(CH₂)₀₋₂; Q = bond, SO₂, CO; E = CH(OH), CO, O, S, CO₂, NR₂, CONR₂; Het = stable, (un)saturated, (un)substituted, 5- to 7-membered mono- or 7- to 10-membered bicyclic heterocyclyl] and salts are prepared. The antagonists (no data) are claimed useful for treatment of disorders such as benign prostatic hypertrophy, peripheral vascular disease, congestive heart failure, and hypertension. For example, cyclocondensation of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde with tosylmethyl isocyanide in MeOH in the presence of K₂CO₃ gave I [X = 7-Cl, R = Me, A = S, Y = bond, Het = 5-oxazolyl], isolated as the HCl salt. Approx. 50 compds. (free bases and/or salts) were prepared in 32 synthetic examples. Three standard formulations are given.

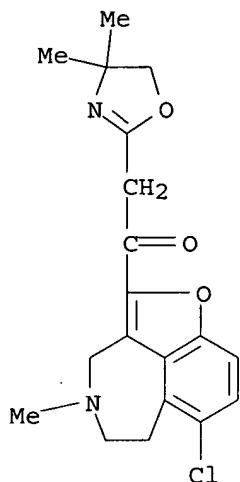
IT 162781-93-3P 162781-94-4P 162781-97-7P

162781-98-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (preparation of tetrahydrothieno- and tetrahydrofurobenzazepine derivs. as α- adrenergic antagonists)

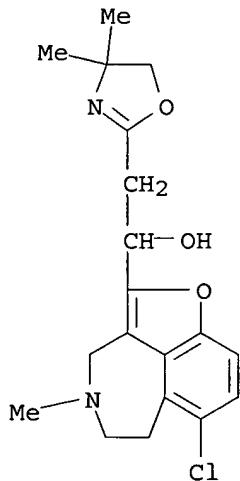
RN 162781-93-3 HCAPLUS

CN Ethanone, 1-(7-chloro-3,4,5,6-tetrahydro-4-methylfuro[4,3,2-ef] [3]benzazepin-2-yl)-2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)- (9CI) (CA INDEX NAME)



RN 162781-94-4 HCAPLUS

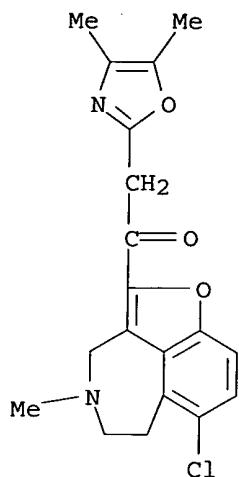
CN Furo[4,3,2-ef][3]benzazepine-2-methanol, 7-chloro-α-[(4,5-dihydro-4,4-dimethyl-2-oxazolyl)methyl]-3,4,5,6-tetrahydro-4-methyl- (9CI) (CA INDEX NAME)



RN 162781-97-7 HCAPLUS

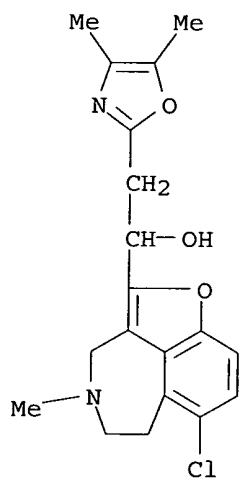
CN Ethanone, 1-(7-chloro-3,4,5,6-tetrahydro-4-methylfuro[4,3-ef][3]benzazepin-

2-yl)-2-(4,5-dimethyl-2-oxazolyl)- (9CI) (CA INDEX NAME)



RN 162781-98-8 HCPLUS

CN Furo[4,3,2-ef][3]benzazepine-2-methanol, 7-chloro-alpha-[(4,5-dimethyl-2-oxazolyl)methyl]-3,4,5,6-tetrahydro-4-methyl- (9CI) (CA INDEX NAME)

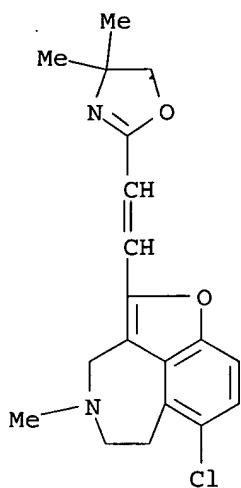


IT 162781-95-5P 162781-96-6P 162781-99-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of tetrahydrothieno- and tetrahydrofurobenzazepine derivs. as α-adrenergic antagonists)

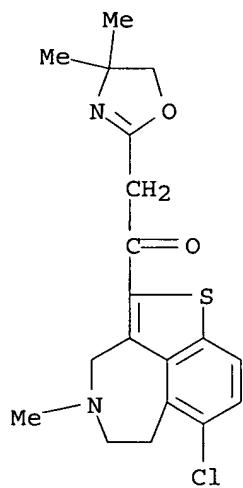
RN 162781-95-5 HCPLUS

CN Furo[4,3,2-ef][3]benzazepine, 7-chloro-2-[2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)ethenyl]-3,4,5,6-tetrahydro-4-methyl- (9CI) (CA INDEX NAME)



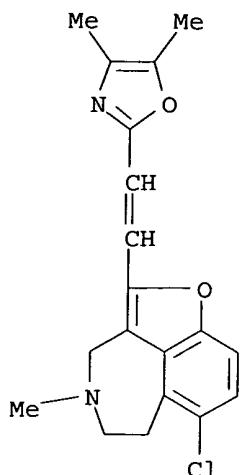
RN 162781-96-6 HCAPLUS

CN Ethanone, 1-(7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef] [3]benzazepin-2-yl)-2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)- (9CI) (CA INDEX NAME)

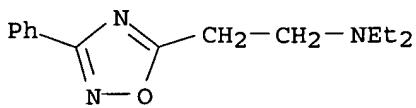


RN 162781-99-9 HCAPLUS

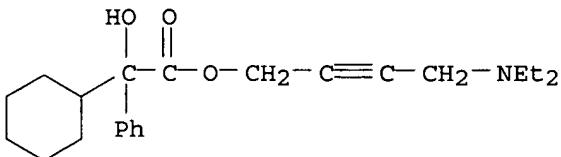
CN Furo[4,3,2-ef][3]benzazepine, 7-chloro-2-[2-(4,5-dimethyl-2-oxazolyl)ethenyl]-3,4,5,6-tetrahydro-4-methyl- (9CI) (CA INDEX NAME)



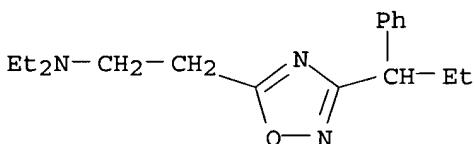
L61 ANSWER 58 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1994:644897 HCPLUS
 DOCUMENT NUMBER: 121:244897
 TITLE: Qualitative organic analysis. Part 3. Identification of drugs and their metabolites by PCA of standardized TLC data
 AUTHOR(S): Romano, Guido; Caruso, Giuseppe; Musumarra, Giuseppe;
 Pavone, Didier; Cruciani, Gabriele
 CORPORATE SOURCE: Istituto di Medicina Legale e delle Assicurazioni,
 Univ. Catania, Catania, 95124, Italy
 SOURCE: Journal of Planar Chromatography--Modern TLC (1994), 7(3), 233-41
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Principal components anal. (PCA) of standardized RF values of 443 drugs and their metabolites present in urine and blood samples chromatographed with four sheet systems provided a two-component model accounting for 70.8% of the total variance. The "scores" plot enabled either identification, or restriction of the range of inquiry to few candidates. This simple, cheap and fast anal. method is of vital importance in the identification of an unknown drug in cases of overdose intoxication or poisoning.
 IT 959-14-8, Oxolamine 5633-20-5, Oxybutynin
 5696-09-3, Proxazole 19216-56-9, Prazosin
 63590-64-7, Terazosin 74191-85-8,
 Doxazosin
 RL: ANT (Analyte); ANST (Analytical study)
 (identification of drugs and metabolites in blood and urine by principal components anal. of standardized thin-layer chromatog. data)
 RN 959-14-8 HCPLUS
 CN 1,2,4-Oxadiazole-5-ethanamine, N,N-diethyl-3-phenyl- (9CI) (CA INDEX NAME)



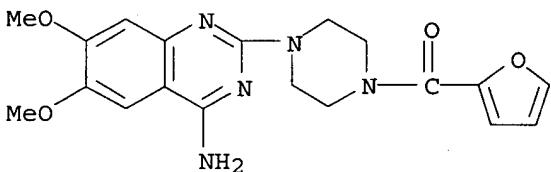
RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



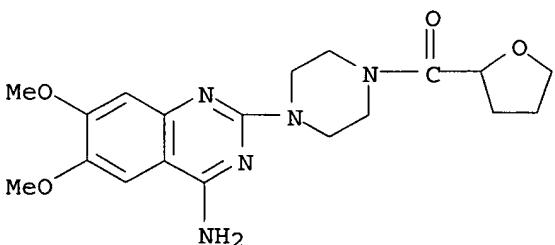
RN 5696-09-3 HCAPLUS
 CN 1,2,4-Oxadiazole-5-ethanamine, N,N-diethyl-3-(1-phenylpropyl)- (9CI) (CA INDEX NAME)



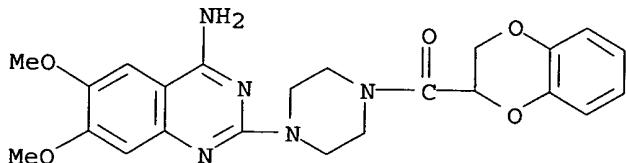
RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)

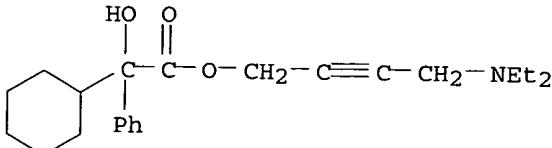


RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 59 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1994:153730 HCAPLUS
 DOCUMENT NUMBER: 120:153730
 TITLE: Synergistic combinations of PAF antagonists and anticholinergic agents as drugs for treatment of bronchial asthma.
 INVENTOR(S): Heuer, Hubert
 PATENT ASSIGNEE(S): Boehringer Ingelheim KG, Germany
 SOURCE: Ger. Offen., 13 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4219659	A1	19931223	DE 1992-4219659	19920616 <--
PRIORITY APPLN. INFO.:			DE 1992-4219659	19920616
OTHER SOURCE(S):	MARPAT 120:153730			
AB	Mixts of htrazepine derivative PAF antagonists (Markush given) with anticholinergics are synergistic drugs for treatment of bronchial asthma. The effectiveness of a combination of atropine with WEB 2170 was shown on PAF-induced bronchoconstriction, in guinea pigs.			
IT	5633-20-5D, Oxybutynin, mixts. with htrazepine derivative PAF antagonists 118196-11-5D, Ym 461, mixts. with anticholinergics 131888-54-5D, Ym 264, mixts. with anticholinergics			
RL:	BIOL (Biological study) (drugs for treatment of bronchial asthma, synergistic)			
RN	5633-20-5 HCAPLUS			
CN	Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)			



RN 118196-11-5 HCAPLUS
 CN Piperazine, 1-(3-phenylpropyl)-4-[(2-(3-pyridinyl)-4-

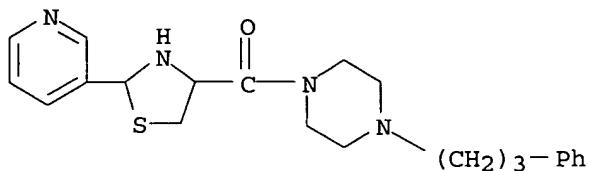
Jones 10_768953

thiazolidinyl]carbonyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 118196-10-4

CMF C22 H28 N4 O S

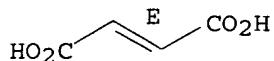


CM 2

CRN 110-17-8

CMF C4 H4 O4

Double bond geometry as shown.



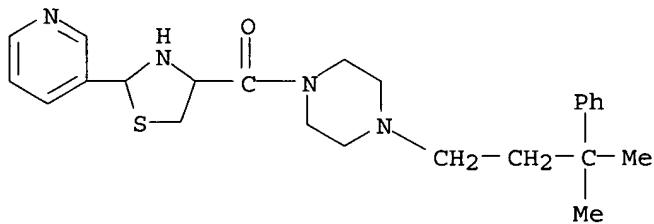
RN 131888-54-5 HCPLUS

CN Piperazine, 1-(3-methyl-3-phenylbutyl)-4-[(2-(3-pyridinyl)-4-thiazolidinyl]carbonyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 126911-71-5

CMF C24 H32 N4 O S

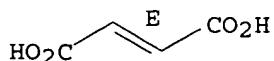


CM 2

CRN 110-17-8

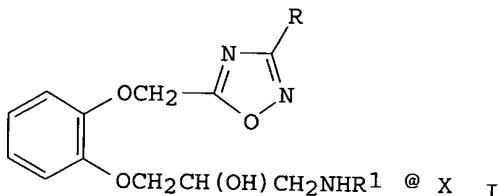
CMF C4 H4 O4

Double bond geometry as shown.



L61 ANSWER 60 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1994:107022 HCPLUS
 DOCUMENT NUMBER: 120:107022
 TITLE: Derivatives of 5-phenoxyethyl-1,2,4-oxadiazole, their salts, method of obtaining them and a pharmaceutical preparation with antihypertensive, antianginal, antiarrhythmic and antiglaucomatous properties based on them
 INVENTOR(S): Sokolov, Sergei Dmitrievich; Vinogradova, Svetlana Mikhailov; Azarevich, Olga Gennadievna; Berg, Marina Valentinovna; Mashkovsky, Mikhail Davydovich; Juzhakov, Sergei Danilovich; Morozov, Aleksandr Vladimirovich; Rozenshtraukh, Leonid Valentino; Medvedev, Oleg Stefanovich; et al.
 PATENT ASSIGNEE(S): Center of Chemical and Medical Equipment, USSR; All-Union Cardiological Research Center; Moscow Scientific-Research Institute of Ophthalmic Diseases PCT Int. Appl., 50 pp.
 SOURCE: CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Russian
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	-----	-----	-----	-----
WO 9309106	A1	19930513	WO 1991-SU215	19911028 <--
W: FI, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
PRIORITY APPLN. INFO.:			WO 1991-SU215	19911028
OTHER SOURCE(S): GI		CASREACT 120:107022; MARPAT 120:107022		

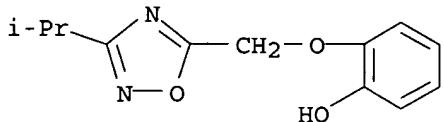


AB Title compds. I (R = Me, Et, iso-Pr, benzyl, Ph; R1 = iso-Pr, tert-Bu, CHMeEt, CH₂CH₂NHCOCHMe₂; X = inorg. or organic acid, or is absent) were prepared by heterocyclization of 1,4-benzodioxin-2(3H)-one with amidoximes RC(:NOH)NH₂ (R as above), followed by alkylation of the resultant 5-(2-hydroxyphenoxyethyl)-1,2,4-oxadiazoles with epichlorohydrin, and aminolysis of the resulting epoxides with R₁NH₂ (R₁ as above). Thus, reaction of 1,4-benzodioxin-2(3H)-one with acetamidoxime afforded 75 mass % 3-methyl-5-(2-hydroxyphenoxyethyl)-1,2,4-oxadiazole; subsequent epichlorohydrin, tert-BuNH₂, and HCl treatment afforded title compound I (R = Me, R₁ = tert-Bu, X = HCl) (II). β -Blocking activity of II in rats (ED₅₀ mg/kg): 0.008 (blocking of depressive activity), 0.03 (blocking of chronotropic activity); α -blocking activity of II in rats: 76% blocking at 10 mg/kg. Formulations of II in tablet, injection solution, and eye-drop form were given.

IT 152289-78-6

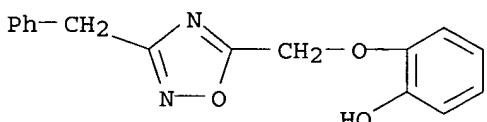
RL: RCT (Reactant); RACT (Reactant or reagent)
 (alkylation of, in preparation of adrenergic antagonists
)

RN 152289-78-6 HCPLUS
 CN Phenol, 2-[[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]methoxy]- (9CI) (CA INDEX NAME)

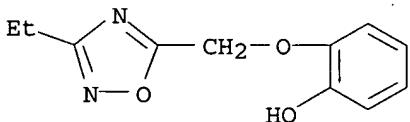


IT 152289-70-8P 152289-74-2P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and alkylation of, in preparation of adrenergic antagonists)

RN 152289-70-8 HCPLUS
 CN Phenol, 2-[[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]methoxy]- (9CI) (CA INDEX NAME)

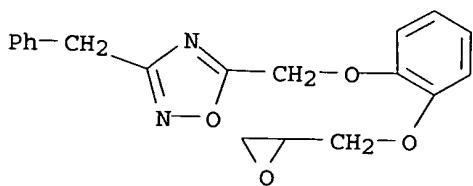


RN 152289-74-2 HCPLUS
 CN Phenol, 2-[(3-ethyl-1,2,4-oxadiazol-5-yl)methoxy]- (9CI) (CA INDEX NAME)

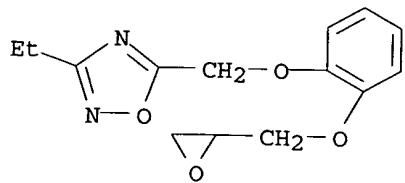


IT 152289-71-9P 152289-75-3P 152289-79-7P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and aminolysis of, in preparation of adrenergic antagonists)

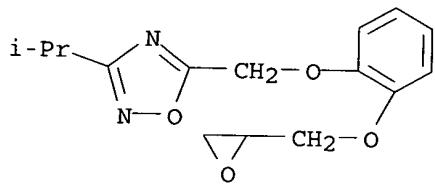
RN 152289-71-9 HCPLUS
 CN 1,2,4-Oxadiazole, 5-[[2-(oxiranylmethoxy)phenoxy]methyl]-3-(phenylmethyl)- (9CI) (CA INDEX NAME)



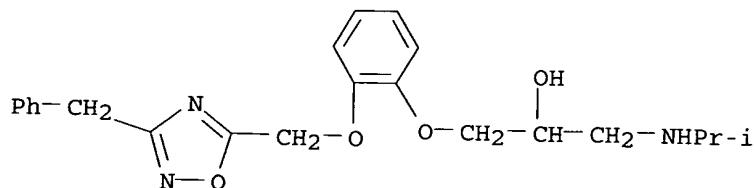
RN 152289-75-3 HCAPLUS
 CN 1,2,4-Oxadiazole, 3-ethyl-5-[[2-(oxiranylmethoxy)phenoxy]methyl]- (9CI)
 (CA INDEX NAME)



RN 152289-79-7 HCAPLUS
 CN 1,2,4-Oxadiazole, 3-(1-methylethyl)-5-[[2-(oxiranylmethoxy)phenoxy]methyl]- (9CI) (CA INDEX NAME)



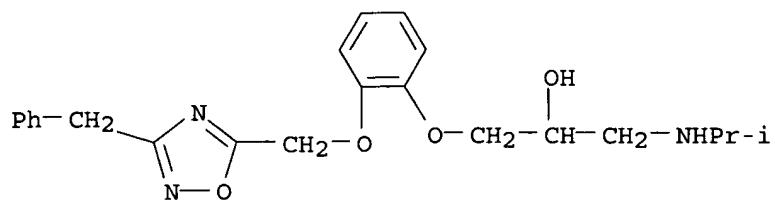
IT 152289-72-0P 152289-73-1P 152289-80-0P
 152289-81-1P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of, as adrenergic antagonist)
 RN 152289-72-0 HCAPLUS
 CN 2-Propanol, 1-[(1-methylethyl)amino]-3-[[2-[[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]methoxy]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

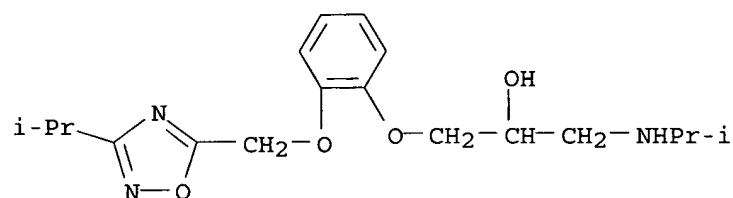
RN 152289-73-1 HCPLUS

CN 2-Propanol, 1-[(1-methylethyl)amino]-3-[2-[[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]methoxy]phenoxy]- (9CI) (CA INDEX NAME)



RN 152289-80-0 HCPLUS

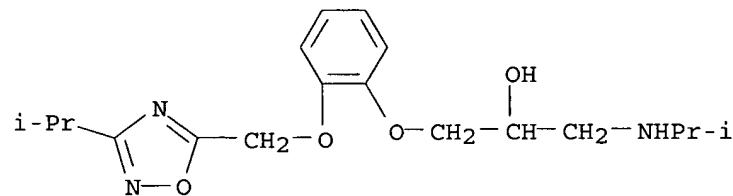
CN 2-Propanol, 1-[(1-methylethyl)amino]-3-[2-[[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]methoxy]phenoxy]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 152289-81-1 HCPLUS

CN 2-Propanol, 1-[(1-methylethyl)amino]-3-[2-[[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]methoxy]phenoxy]- (9CI) (CA INDEX NAME)

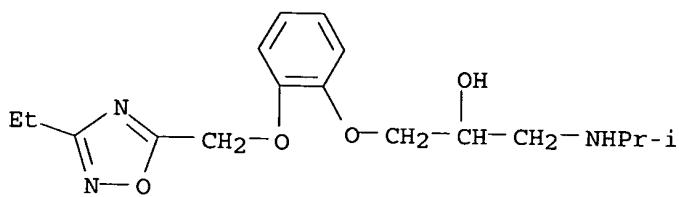


IT 152289-76-4P 152289-77-5P 152726-44-8P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as adrenergic antagonists)

RN 152289-76-4 HCPLUS

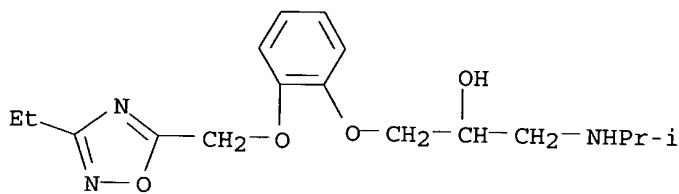
CN 2-Propanol, 1-[2-[(3-ethyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-3-[(1-methylethyl)amino]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 152289-77-5 HCPLUS

CN 2-Propanol, 1-[2-[(3-ethyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-3-[(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



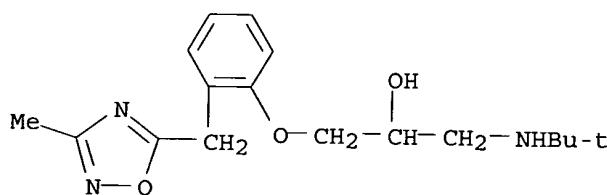
RN 152726-44-8 HCPLUS

CN 2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[2-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]phenoxy]-, (2Z)-2-butenedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 152726-43-7

CMF C17 H25 N3 O3

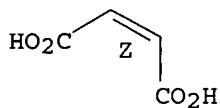


CM 2

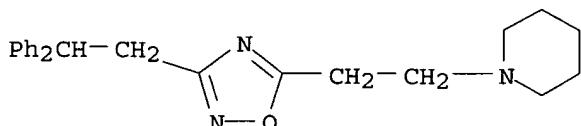
CRN 110-16-7

CMF C4 H4 O4

Double bond geometry as shown.

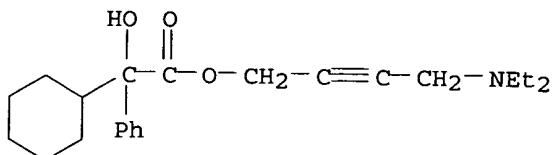


L61 ANSWER 61 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1992:604537 HCAPLUS
 DOCUMENT NUMBER: 117:204537
 TITLE: Reversal of multidrug resistance by phenothiazines and structurally related compounds
 AUTHOR(S): Ramu, Avner; Ramu, Nili
 CORPORATE SOURCE: Dep. Oncol., Hadassah Univ. Hosp., Jerusalem, 91 120, Israel
 SOURCE: Cancer Chemotherapy and Pharmacology (1992), 30(3), 165-73
 CODEN: CCPHDZ; ISSN: 0344-5704
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The multidrug-resistance (MDR)-reversal activity of 232 phenothiazines and structurally related compds. was tested in MDR P388 cells. Such activity was found among compds. exhibiting two ring structures (Ph, cyclopentyl, cyclohexyl, thiienyl or 5-norbornen-2-yl but not pyridinyl) linked by a variety of bridge types and possessing a secondary or tertiary amine group. Among 192 such compds., 31.8% displayed good activity (MDR-reversal ratio, ≥10) and 8.3%, outstanding activity (MDR-reversal ratio, ≥30). In a subgroup comprising 56 compds. with a carbonyl residue, 4 with sulfuryl residue and 1 with thiienyl residue, 42.7% showed good activity and 18%, outstanding activity. The contribution of these residues to the MDR-reversal activity was particularly evident among compds. containing a cyclic tertiary amine. Among 49 such compds., 51% displayed good activity and 20.4%, outstanding activity, whereas among the 85 compds. lacking such groups, only 31.8% showed good activity and 4.7%, outstanding activity. Enhancement of this activity by the carbonyl group is also obtained when the latter is part of an amide bond of a tertiary amine. As compds. with a carbonyl group located on the rings, on the bridge to the amine group or beyond the amine are efficient MDR reversers, it seems that the exact mol. location of the carbonyl group is not critical for the elicitation of this activity.
 IT 982-43-4, Prenoxdiazine 5633-20-5, Oxybutynin
 RL: BIOL (Biological study)
 (multidrug resistance reversal by, structure in relation to)
 RN 982-43-4 HCAPLUS
 CN Piperidine, 1-[2-[3-(2,2-diphenylethyl)-1,2,4-oxadiazol-5-yl]ethyl]-, monohydrochloride (8CI, 9CI) (CA INDEX NAME)



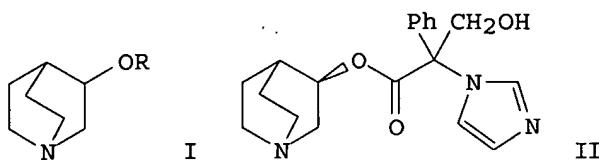
● HCl

RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



L61 ANSWER 62 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1992:511614 HCAPLUS
 DOCUMENT NUMBER: 117:111614
 TITLE: Preparation of quinuclidinyl 2-heterocyclalkyl-3-hydroxy-2-phenylpropanoates as antimuscarinic bronchodilators
 INVENTOR(S): Stobie, Alan
 PATENT ASSIGNEE(S): Pfizer Ltd., UK; Pfizer Inc.
 SOURCE: PCT Int. Appl., 89 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9204346	A1	19920319	WO 1991-EP1670	19910903 <--
W: CA, FI, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2073005	AA	19920307	CA 1991-2073005	19910903 <--
CA 2073005	C	19981110		
EP 500864	A1	19920902	EP 1991-915623	19910903 <--
EP 500864	B1	20010919		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05502454	T2	19930428	JP 1991-513922	19910903 <--
JP 07025756	B4	19950322		
AT 205844	E	20011015	AT 1991-915623	19910903 <--
ES 2161211	T3	20011201	ES 1991-915623	19910903 <--
FI 9202013	A	19920505	FI 1992-2013	19920505 <--
FI 97469	B	19960913		
FI 97469	C	19961227		
US 5292749	A	19940308	US 1992-852261	19920605 <--
PRIORITY APPLN. INFO.:			GB 1990-19472	A 19900906
			GB 1991-6733	A 19910328
OTHER SOURCE(S): GI			WO 1991-EP1670	W 19910903



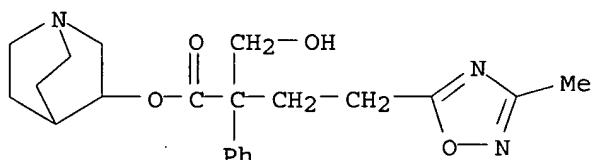
AB Title compds. [I; R = COCX(CH₂OH)(CH₂)_mR₁; R₁ = (substituted) imidazolyl, -triazolyl, -oxadiazolyl, -pyridyl, -pyrimidinyl, etc.; X = thieryl, (substituted) Ph; m = 1, 2] were prepared as bronchodilators (no data). Thus, CH₂:CPhCO₂H was esterified by (R)-3-quinuclidinol and the product treated with imidazole, HCHO, and NaH to give title compds. (R)- and (S)-II.

IT 141831-40-5P 141831-41-6P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antimuscarinic bronchodilator)

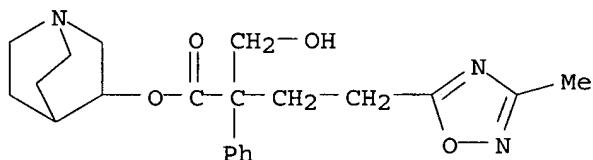
RN 141831-40-5 HCPLUS

CN 1,2,4-Oxadiazole-5-butanoic acid, α -(hydroxymethyl)-3-methyl- α -phenyl-, 1-azabicyclo[2.2.2]oct-3-yl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)



RN 141831-41-6 HCPLUS

CN 1,2,4-Oxadiazole-5-butanoic acid, α -(hydroxymethyl)-3-methyl- α -phenyl-, 1-azabicyclo[2.2.2]oct-3-yl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)



L61 ANSWER 63 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:598429 HCPLUS

DOCUMENT NUMBER: 115:198429

TITLE: The effect of α 1-acid glycoprotein on the pharmacological activity of α 1-adrenergic antagonists in rabbit aortic strips

AUTHOR(S): Chiang, Janie; Hermodsson, Gorel; Oie, Svein

CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA

SOURCE: Journal of Pharmacy and Pharmacology (1991), 43(8), 540-7

CODEN: JPPMAB; ISSN: 0022-3573

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB The pharmacol. activity of three α 1- adrenergic antagonists, prazosin, tiotiazosin and WB4101, has been studied in the presence and absence of 10 μ M α 1-acid glycoprotein (AAG) in rabbit aortic strips, and measured as the ability to increase the EC50 value of the α 1-adrenergic agonist phenylephrine. For all three drugs, the presence of AAG diminished the pharmacol. activity when compared with equivalent unbound concns. in the absence of AAG. In the presence of AAG, the EC50 value of phenylephrine at 5.69 nM unbound prazosin was on average 47% lower than in the absence of AAG, at 122 nM unbound tiotiazosin, 39% lower, and at 25.6 nM unbound AB4101, 68% lower. Albumin showed no ability to modify the α 1-adrenergic blocking activity of prazosin. The EC50 value for phenylephrine in the absence of antagonists was not affected by AAG. The effect of AAG on the antagonistic activity of prazosin was concentration-dependent with a maximum suppression of prazosin activity of 79% and with a half-maximum concentration of 1.1 μ M AAG. AAG decreased prazosin's ability to reduce α 3-adrenergic stimulation of calcium influx, while it had no effect on prazosin's ability to decrease α 1-adrenergic-stimulated formation of inositol phosphate. These results suggest that the effect of AAG on adrenoceptors appears to act selectively via α 1a-receptors. Consistent with these observations was the observation that WB4101, a selective α 1a-antagonist was more affected by AAG than was prazosin or tiotiazosin.

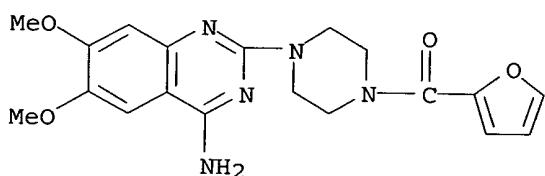
IT 19216-56-9, Prazosin 66969-81-1, Tiotiazosin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacol. of, as α - adrenergic antagonist, in aorta, α 1-acid glycoproteins effect on)

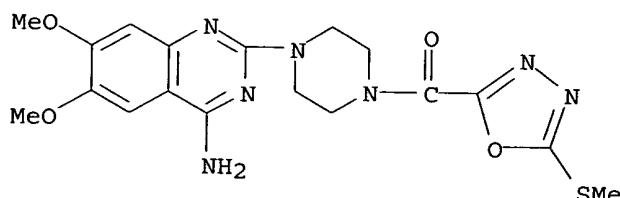
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)

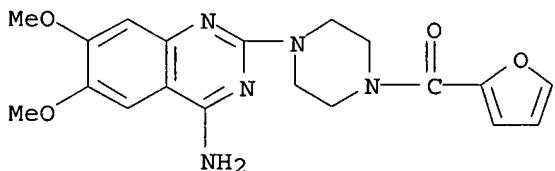


RN 66969-81-1 HCAPLUS

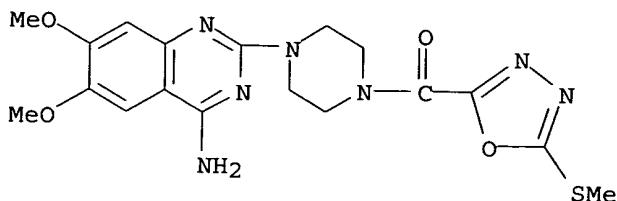
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 64 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1989:490254 HCAPLUS
 DOCUMENT NUMBER: 111:90254
 TITLE: Alteration in the pharmacologic activity of α 1 adrenergic antagonists by alpha-1-acid glycoprotein
 AUTHOR(S): Oie, Svein; Chiang, Janie
 CORPORATE SOURCE: Dep. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
 SOURCE: Progress in Clinical and Biological Research (1989), Volume Date 1988, 300(Alpha1-Acid Glycoprotein), 235-8
 CODEN: PCBRD2; ISSN: 0361-7742
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Changes in EC50 of phenylephrine by α 1-antagonists (prazosin, tiadiazosin, and WB 4101) in the absence and presence of α 1-acid glycoprotein (AAG) and albumin were studied in isolated aortic preparation AAG muted the effect of the α 1 adrenergic antagonists as the activity in the presence of AAG is lower than in the absence of AAG at identical unbound concns. In contrast, albumin had no effect on the activity of prazosin in unbound concns. AAG alone at \leq 40 μ m had no effect on the isometric contraction of aortic strips. In rats, AAG alone had no effect on the blood pressure. Rats given 40 mg AAG/kg followed by a bolus dose of 160 μ g prazosin/kg and those given 40 mg AAG/kg followed by a 50-100 μ g prazosin/kg bolus dose showed an approx. 2-fold lower effect (percent change in the systolic blood pressure from pre-prazosin administration) at the same unbound concns. when compared with animals given 160 μ g prazosin/kg and 50-100 μ g/kg bolus dose of prazosin followed by a constant infusion of 0.6-2.4 kg prazosin.
 IT 19216-56-9, Prazosin 66969-81-1, Tiadiazosin
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmacol. of, orosomucoid effect on)
 RN 19216-56-9 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 66969-81-1 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl-(9CI) (CA INDEX NAME)



L61 ANSWER 65 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:491121 HCPLUS

DOCUMENT NUMBER: 105:91121

TITLE:

The potency of α -adrenoceptor antagonists at the α_1 -adrenoceptors of the rat anococcygeus muscle

Doggrell, S. A.; Edmonds, S. C.

CORPORATE SOURCE: Sch. Med., Univ. Auckland, Auckland, N. Z.

SOURCE: Pharmacol. Adrenoceptors, [Proc. Satell. Symp.] (1985), Meeting Date 1984, 277-8. Editor(s): Szabadi, Elmer; Bradshaw, Christopher M.; Nahorski, S. R. Macmillan: Basingstoke, UK.

CODEN: 55CBAB

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Contractile responses of isolated rat anococcygeus muscle to phenylephrine (a α_1 -agonist) were inhibited by E 643 [52712-76-2], prazosin [19216-56-9], doxazosin [74191-85-8], WB 4101 [613-67-2], phentolamine [50-60-2], indoramin [26844-12-2], tiotiazosin [66969-81-1], CGS 7525 A [71576-41-5], corynanthine [483-10-3], trimazosin [35795-16-5], yohimbine [146-48-5], rauwolscine [131-03-3], idazoxan [79944-58-4], and L-644 [85386-84-1]; methacholine-induced contraction was not affected by these drugs. The order of potency as antagonists at the α_1 -adrenoceptors was WB 41014 \geq E 643 \geq prazosin > doxazosin > phentolamine \geq indoramin > tiotiazosin > CGS 7525 A > corynanthine \geq trimazosin \geq yohimbine > rauwolscine \geq idazoxan > L-644. These results are discussed in relation to characterization of α_2 -receptors.

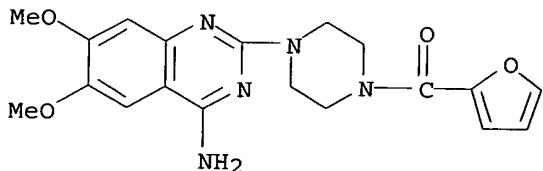
IT 19216-56-9 66969-81-1 74191-85-8

RL: BIOL (Biological study)

(anococcygeus muscle contraction response to)

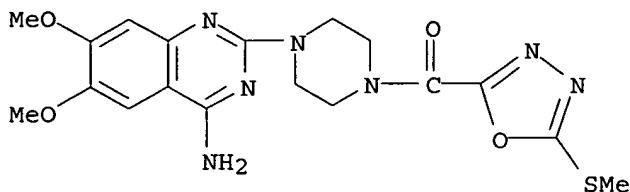
RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)

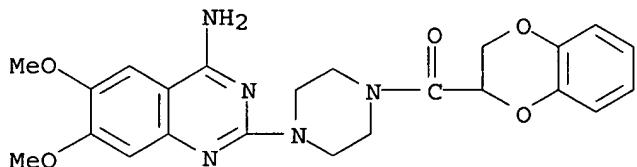


RN 66969-81-1 HCPLUS

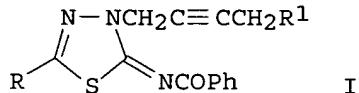
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(5-(methylthio)-1,3,4-oxadiazol-2-yl)carbonyl]-(9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)

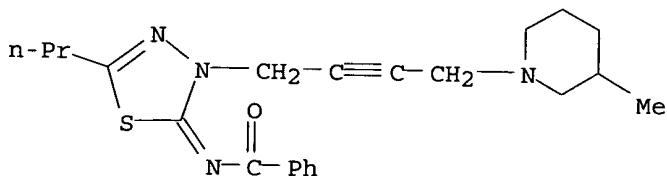


L61 ANSWER 66 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1986:490805 HCAPLUS.
 DOCUMENT NUMBER: 105:90805
 TITLE: Synthesis and biological evaluation of
 N-[5-alkyl-3-(4-tert-amino-2-butynyl)-1,3,4-thiadiazol-
 2(3H)-ylidene]benzamides
 AUTHOR(S): Muhi-Eldeen, Zuhair; Hadi, Ali; Al-Shamma, Ali;
 Salman, Salman Rashed; Sameh, Inam; Falih, Nidhal
 CORPORATE SOURCE: Coll. Pharm., Univ. Baghdad, Baghdad, Iraq
 SOURCE: European Journal of Medicinal Chemistry (1986
), 21(3), 219-23
 CODEN: EJMCA5; ISSN: 0223-5234
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 105:90805
 GI

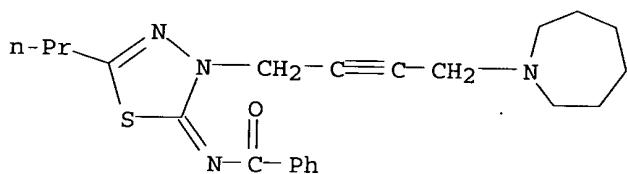


AB A series of 16 title compds. I (R = Me, or Pr; R¹ = piperidino, perhydroazepino, morpholino, etc.) were prepared and investigated for blocking of the motor effects of oxotremorine [70-22-4] (a muscarinic agonist) in mice. All of the prepared derivs. showed a weak muscarinic antagonistic activity comparable to that of their corresponding 1,3,4-thiadiazol-2(3H)-one derivs.
 IT 103811-57-0P 103826-74-0P 103826-75-1P
 103826-76-2P 103826-85-3P 103839-53-8P
 103839-54-9P 103839-55-0P
 RL: SPN (Synthetic preparation); PREP (Preparation)

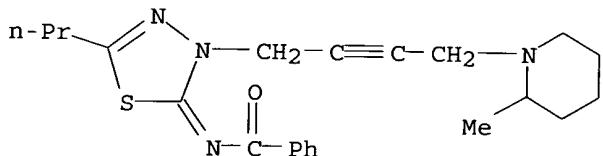
(preparation and antimuscarinic activity of)
 RN 103811-57-0 HCAPLUS
 CN Benzamide, N-[3-[4-(3-methyl-1-piperidinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



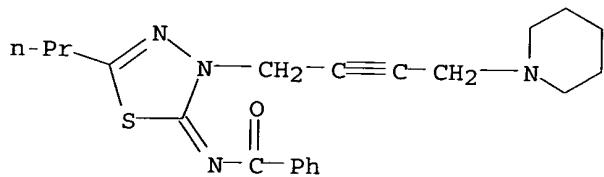
RN 103826-74-0 HCAPLUS
 CN Benzamide, N-[3-[4-(hexahydro-1H-azepin-1-yl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



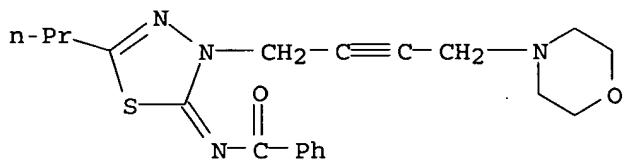
RN 103826-75-1 HCAPLUS
 CN Benzamide, N-[3-[4-(2-methyl-1-piperidinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



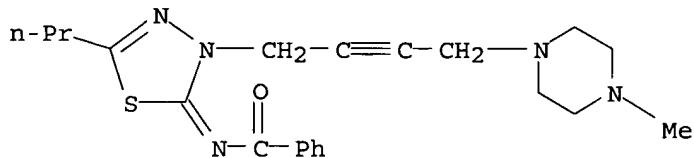
RN 103826-76-2 HCAPLUS
 CN Benzamide, N-[3-[4-(1-piperidinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



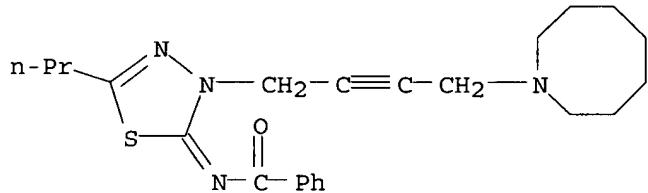
RN 103826-85-3 HCAPLUS
 CN Benzamide, N-[3-[4-(4-morpholinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



RN 103839-53-8 HCAPLUS
 CN Benzamide, N-[3-[4-(4-methyl-1-piperazinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)

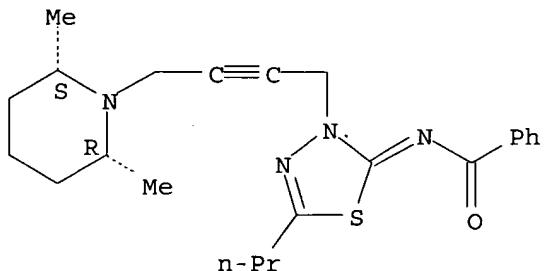


RN 103839-54-9 HCAPLUS
 CN Benzamide, N-[3-[4-(hexahydro-1(2H)-azocinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]- (9CI) (CA INDEX NAME)



RN 103839-55-0 HCAPLUS
 CN Benzamide, N-[3-[4-(2,6-dimethyl-1-piperidinyl)-2-butynyl]-5-propyl-1,3,4-thiadiazol-2(3H)-ylidene]-, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.
 Double bond geometry unknown.



L61 ANSWER 67 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1985:178711 HCAPLUS
 DOCUMENT NUMBER: 102:178711
 TITLE: Recirculatory moment analysis of drugs in man:
 estimation of extraction ratio and mean cycle time for

AUTHOR(S): single systemic and pulmonary circulation
 Yamaoka, Kiyoshi; Nakagawa, Terumichi; Tanaka, Hisashi
 CORPORATE SOURCE: Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606, Japan
 SOURCE: Chemical & Pharmaceutical Bulletin (1985),
 33(2), 784-94

DOCUMENT TYPE: CODEN: CPBTAL; ISSN: 0009-2363
 Journal
 LANGUAGE: English

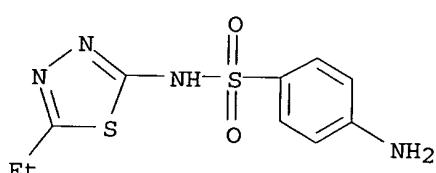
AB The extraction ratio (E_c) and the mean cycle times (.hivin.tc) for single systemic and pulmonary circulation were evaluated for 115 drugs in man. Heparin [9005-49-6] and fluorohydrocortisone [127-31-1], which have the smallest .hivin.tc values (about 1 min) had the small E_c values (close to zero). This result suggests that these drugs circulate through the body restricted within the blood vessels. The theor. considerations indicate that the clearances defined by $A_i(\infty)/AUC$ differ from E_iQ_i , where $A_i(\infty)$ is the amount eliminated by organ i , AUC is the area under the plasma concentration curve, E_i is the extraction ratio and Q_i is plasma flow rate

through organ i . The hepatic extraction ratios (E_h) of alprenolol, metoprolol and propranolol calculated from i.v. data alone are large (>80%). It is also shown that the steady-state volume of distribution (V_{ss}) is rather independent of hepatic and renal extraction ratios, while the mean residence time is considerably affected by change of these ratios.

IT 94-19-9 19216-56-9
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (pharmacokinetics of, recirculatory moment anal. in humans in)

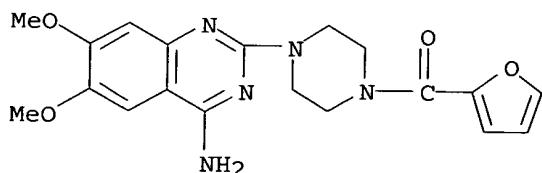
RN 94-19-9 HCPLUS

CN Benzenesulfonamide, 4-amino-N-(5-ethyl-1,3,4-thiadiazol-2-yl)- (9CI) (CA INDEX NAME)



RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



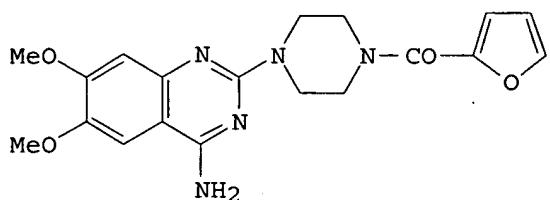
L61 ANSWER 68 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1983:605840 HCPLUS

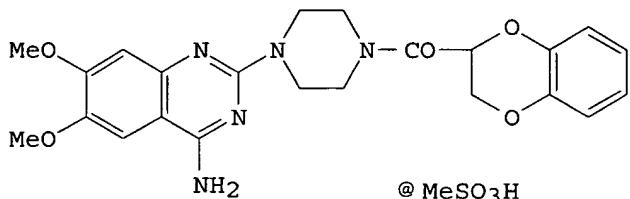
DOCUMENT NUMBER: 99:205840

TITLE: Noncompetitive antagonism of the α -adrenoceptor-mediated fast component of contraction of rat aorta by

AUTHOR(S): doxazosin and prazosin
 Downing, O. A.; Wilson, K. A.; Wilson, V. G.
 CORPORATE SOURCE: Dep. Pharm., Univ. Aston, Birmingham, B4 7ET, UK
 SOURCE: British Journal of Pharmacology (1983),
 80(2), 315-22
 CODEN: BJPCBM; ISSN: 0007-1188
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



I

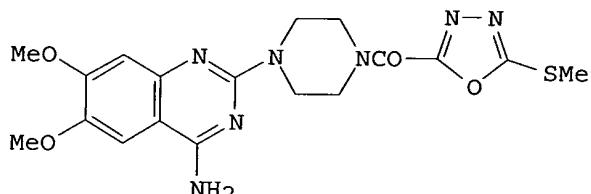


II

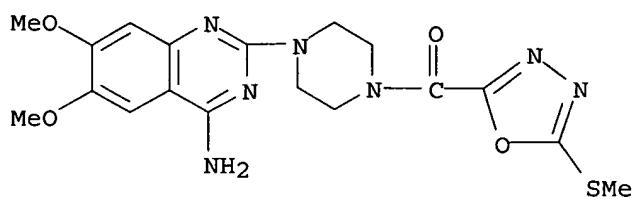
AB α-Adrenoceptor antagonists were compared for their effects on dose-response curves of fast and slow components of contraction of the rat aorta to noradrenaline (NA). All agents caused a competitive antagonism of the slow component of contraction to NA. The order of potency was: prazosin (I) [19216-56-9] > WB4101 [613-67-2] = doxazosin mesylate (II) [77883-43-3] > tirodazosin levulinate [76798-65-7] > phentolamine mesylate [65-28-1] > corynanthine [483-10-3] > trimazosin [35795-16-5] > rauwolscine [131-03-3]. For the fast component, doxazosin, prazosin, tirodazosin, and WB4101 caused some depression of the maximum response. Doxazosin (25 nM) and prazosin (25 nM) produced a complete antagonism of the maximum fast component. Phentolamine, corynanthine, trimazosin, and rauwolscine all competitively antagonized the fast component. The degree of antagonism of the fast component by prazosin and its analogs appeared to be directly related to the potency of individual agents for the slow component. WB4101, which was equipotent with doxazosin and more potent than tirodazosin was less effective than either in reducing the fast component. The antagonism of the fast component by prazosin or doxazosin was easily reversed by washing and prevented by phentolamine (2.5 μM). Neither prazosin nor doxazosin in concns. of up to 2.5 μM had any effect on contractions of the aorta to 5-HT (0.25-250 μM) or caffeine (20 mM). Thus, the ability of some α-adrenoceptor antagonists to produce a noncompetitive antagonism of the fast component of contraction is (a) dependent upon blockade of α-adrenoceptors; (b) unrelated to selectivity for α₁-adrenoceptors; and (c) related to potency and structure. EGTA (3.0 mM) caused a selective suppression of the slow component of contraction to NA. Both doxazosin and

prazosin caused a noncompetitive antagonism of EGTA-resistant contractions to NA, whereas corynanthine showed competitive antagonism. Apparently, prazosin and doxazosin noncompetitively antagonize α -adrenoceptor-induced release of Ca in the rat aorta, but competitively antagonize α -adrenoceptor-induced Ca entry.

L61 ANSWER 69 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1983:204298 HCPLUS
 DOCUMENT NUMBER: 98:204298
 TITLE: The bioavailability and disposition of tirodazosin levulinate in beagle dogs with a comparison to prazosin hydrochloride
 AUTHOR(S): Baughman, Robert A., Jr.; Mico, Bruce A.; Benet, Leslie Z.
 CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, USA
 SOURCE: Drug Metabolism and Disposition (1983), 11(2), 143-6
 DOCUMENT TYPE: CODEN: DMDSAI; ISSN: 0090-9556
 LANGUAGE: Journal
 GI English



- AB tirodazosin (I) [66969-81-1] was administered as I levulinate [76798-65-7] to 5 male beagle dogs at 1 mg/kg both i.v. and as an oral solution. Plasma and whole blood samples were taken serially over 24 h and analyzed with a new specific and sensitive HPLC assay. The half-life of I was significantly shorter than that of prazosin. The calculated bioavailability of I was less than the predicted bioavailability by a factor of 3, whereas prazosin-calculated bioavailability was the same as predicted. Assumptions necessary to predict the bioavailability of compds. cleared by the hepatic route appear to be incorrect for I. Possible mechanisms for the unpredictable low I bioavailability in dogs are presented.
- IT 66969-81-1 76798-65-7
 RL: BIOL (Biological study)
 (bioavailability and pharmacokinetics of, from i.v. and oral solns.)
- RN 66969-81-1 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(5-(methylthio)-1,3,4-oxadiazol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



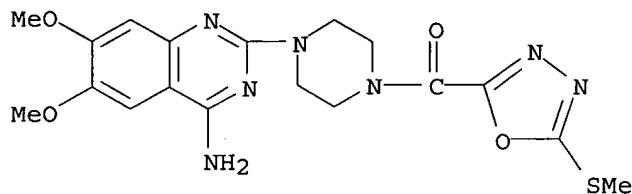
RN 76798-65-7 HCPLUS

CN Pentanoic acid, 4-oxo-, compd. with 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]piperazine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 66969-81-1

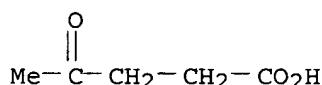
CMF C18 H21 N7 O4 S



CM 2

CRN 123-76-2

CMF C5 H8 O3



L61 ANSWER 70 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1982:433047 HCPLUS

DOCUMENT NUMBER: 97:33047

TITLE: Determination of tiotiazosin in plasma and whole blood by high-performance liquid chromatography

AUTHOR(S): Mico, Bruce A.; Baughman, Robert A., Jr.; Benet, Leslie Z.

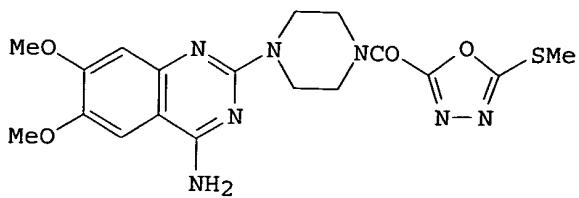
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143, USA

SOURCE: Journal of Chromatography (1982), 230(1), 203-6

DOCUMENT TYPE: CODEN: JOCRAM; ISSN: 0021-9673

LANGUAGE: Journal

GI English



AB tiodazosin (I) [66969-81-1] was determined in whole blood and plasma by high-performance liquid chromatog. MeCN containing the internal standard prazosin was added to deproteinized plasma and whole blood samples, and the samples centrifuged; the supernatants were reduced in volume by evaporation and chromatographed on a C48 reversed-phase column with fluorescence detection at 340 and 384 nm (excitation and emission, resp.). An aqueous solution of 21% MeCN with 0.1% H₃PO₄ was used as the mobile phase

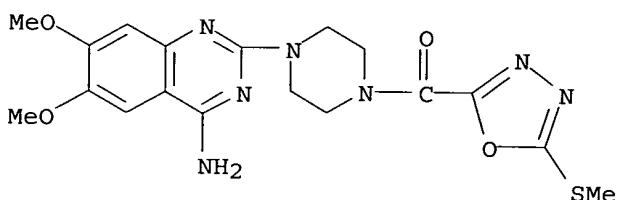
n+H = 3.60). The calibration curves were linear at 6-868 ng I/mL. The pharmacokinetics of I was studied in beagle dogs; apparently, the detection limit (1 ng/mL) achieved in these pharmacokinetic studies could be improved by further refinement of the method.

IT 66969-81-1

RL: ANT (Analyte); ANST (Analytical study)
(determination and pharmacokinetics of, in blood by high-performance liquid chromatog.)

RN 66969-81-1 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 71 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1982:421871 HCPLUS

DOCUMENT NUMBER: 97:21871

TITLE: Antibodies to the α_1 - and α_2 -selective antagonists prazosin and yohimbine as probes of the α -adrenergic binding sites

AUTHOR(S): Graham, Robert M.; Hess, Hans Juergen; Haber, Edgar; Homcy, Charles J.

CORPORATE SOURCE: Cell. Mol. Res. Lab., Massachusetts Gen. Hosp., Boston, MA, 02114, USA

SOURCE: Hypertension (1982), 4(3, Pt. 2), 183-7
CODEN: HPRTDN; ISSN: 0194-911X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antibodies were raised against a newly synthesized analog (CP57,609) of the α_1 -selective antagonist prazosin, and against the α_2 -selective antagonist, yohimbine, by immunization of rabbits with

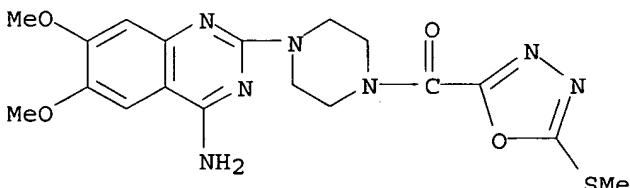
antigens prepared by covalent linkage of these ligands to albumin. Competitive inhibition of [³H]prazosin binding to anti-CP57,609 antiserum by a variety of unlabeled ligands revealed a spectrum of antibody specificity, with α_1 -selective agents competing more potently than α_2 -selective ligands. In contrast, α_2 -selective ligands competed more potently with the binding of [³H]yohimbine to the anti-yohimbine antiserum than α_1 -selective agents. These resp. antisera were subjected to affinity fractionation on a CP57,609- or yohimbine-Sepharose 4B resin. Fractions from the CP57,609 resin were eluted successively with phentolamine (10-3 M), prazosin (10-4 M), and guanidine (5M), and from the yohimbine resin with prazosin (10-4 M), yohimbine (10-4 M), and guanidine (5M). The binding profiles of these fractions differed, and in certain fractions the relative order of potency of adrenergic agents was almost identical to that observed with membrane α -adrenergic receptors. Moreover, using these eluted fractions as immunogens, antisera were obtained which, in the initial bleeds, already possessed antiidiotypic activity. These findings therefore suggest that affinity fractionation of antibodies raised against α_1 - and α_2 -selective antagonists may provide useful analogs for the further study of the ligand recognition properties of α -adrenergic receptors. Addnl., it is probable that antiidiotypic antisera will be developed which will recognize the α -adrenergic binding sites.

IT 62412-39-9

RL: BIOL (Biological study)

(antibody binding to prazosin and yohimbine antagonism by,
 α -adrenergic receptor in relation to)

RN 62412-39-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[[5-(methylthio)-
1,3,4-oxadiazol-2-yl]carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

● HCl

L61 ANSWER 72 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1981:76779 HCPLUS

DOCUMENT NUMBER: 94:76779

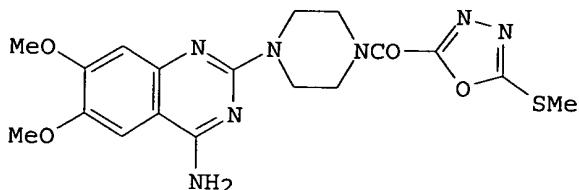
TITLE: Effects of tiotiazosin, prazosin, trimazosin and
phentolamine on blood pressure, heart rate and on pre-
and postsynaptic α -adrenergic receptors in the
ratAUTHOR(S): Buyniski, J. P.; Pircio, A. W.; Schurig, J. E.;
Campbell, J. A.CORPORATE SOURCE: Pharmacol. Dep., Bristol Lab., Syracuse, NY, 13201,
USA

SOURCE: Clinical and Experimental Hypertension (1978-1981) (1980), 2(6), 1039-66

CODEN: CEHYDQ; ISSN: 0148-3927

DOCUMENT TYPE: Journal

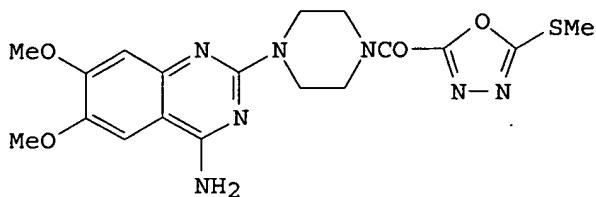
LANGUAGE: English
GI



I

AB S.c. administration of BL-5111A (tiodazosin) (I) [62412-39-9] (0.1-3 mg/kg), prazosin [19216-56-9] (0.01-1 mg/kg), trimazosin [35795-16-5] (10-30 mg/kg) and phentolamine [50-60-2] (0.1-3 mg/kg) to conscious spontaneously hypertensive rats (SHR) produced graded decreases in blood pressure with the order of potency being prazosin > I > phentolamine > trimazosin. Heart rate was elevated predominantly only by phentolamine and this was consistent with the activity of this agent for both pre- and postsynaptic α -adrenergic receptors. In contrast, I, prazosin, and trimazosin showed selectivity only for postsynaptic α -adrenergic receptors. Acute oral administration of I and prazosin indicated I to be about 1/2 as potent as prazosin. However, chronic administration of equivalent doses of the 2 compds. for 25 and 52 days via the drinking water indicated approx. equivalent, sustained redns. in blood pressure. Furthermore, at the end of the 52-day chronic dosing period I caused appreciably less α -adrenergic receptor antagonist activity than prazosin as assessed by the norepinephrine dose-pressor response profiles. Thus, following chronic dosing with I in the rat other mechanisms besides α -adrenergic receptor antagonist activity are probably contributing to the antihypertensive effect in the rat.

L61 ANSWER 73 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1981:76628 HCPLUS
 DOCUMENT NUMBER: 94:76628
 TITLE: In vitro comparison of the pre- and postsynaptic alpha adrenergic receptor blocking properties of prazosin and tiодазосин (BL5111)
 AUTHOR(S): Cohen, Marlene L.; Wiley, Kathryn S.; Landry, Ann Schwab
 CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
 SOURCE: Clinical and Experimental Hypertension (1978-1981) (1980), 2(6), 1067-82
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB BL5111 (tiiodazosin) (I) [66969-81-1], a structural analog of prazosin [19216-56-9] was a potent competitive postsynaptic α -adrenergic receptor antagonist. Although tiiodazosin exhibited an affinity for the postsynaptic α -receptor that was 17 times lower than prazosin, tiiodazosin was still 4 times more potent than phentolamine in this regard. Under in vitro conditions, tiiodazosin, like prazosin, also produced a noncompetitive antagonism of α -adrenergic receptors in the portal vein, did not show marked affinity for presynaptic α -adrenergic receptors, and lacked any measurable direct vasodilator effects (nonreceptor mediated) independent of α -adrenergic receptor blockade.

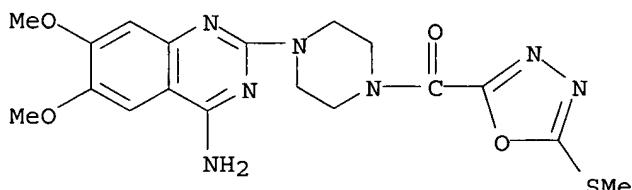
IT 66969-81-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(sympatholytic activity of, prazosin in relation to)

RN 66969-81-1 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(5-(methylthio)-1,3,4-oxadiazol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



L61 ANSWER 74 OF 77 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1980:525499 HCPLUS

DOCUMENT NUMBER: 93:125499

TITLE: Effect of BL-5111-A, prazosin and phentolamine on responses of canine cutaneous veins to adrenergic activation

AUTHOR(S): Rusch, N. J.; De Mey, J. G.; Vanhoutte, P. M.

CORPORATE SOURCE: Fac. Med., Univ. Antwerp, Wilrijk, B-2610, Belg.

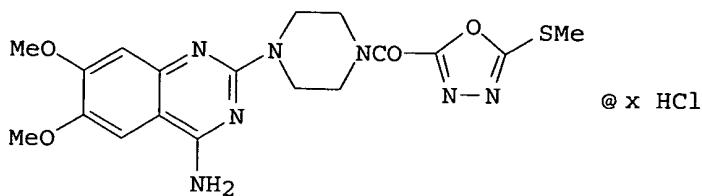
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1980), 244(2), 341-3

CODEN: AIPTAK; ISSN: 0003-9780

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



1

- AB In canine sephenous veins with blocked β -adrenergic receptors, the contractile responses to norepinephrine or elec. stimulation were inhibited, in order of increasing extent, by BL-5111-A (I) [62412-39-9], prazosin [19216-56-9], and phentolamine [50-60-2]. The small effect of I may be due to a specificity for α_1 -receptors and indicates that I should interfere little with venomotor regulation.

L61 ANSWER 75 OF 77 HCAPLUS COPYRIGHT 2006 ACS OR STN

ACCESSION NUMBER: 1980-157747 UCARLUS

ACCESSION NUMBER: 1980:1577
DOCUMENT NUMBER: 83-157743

DOCUMENT NUMBER: 92:157747
TITLE: Profile of a new prazosin congener, BL-5111A. Studies in the rat.

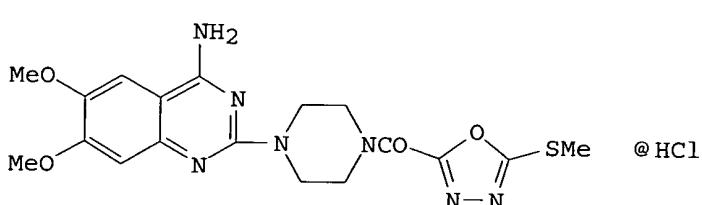
AUTHOR(S): in the rat
Cates, Valerie E., et al.

AUTHOR(S): Oates, Helen F.; Stoker, Lynette M.; Stokes, G. S.
CORPORATE SOURCE: Med. Res. Dep., Sydney Hosp., Sydney, 2000, Australia
SOURCE: Clinical and Experimental Pharmacology and Physiology
(1990), 7(1), 1-8

(1980), 7(1), 1-9
CODEN: SCSPEZ ISSN: 0360-1380

DOCUMENT TYPE: Journal Article CODEN: CEJAD

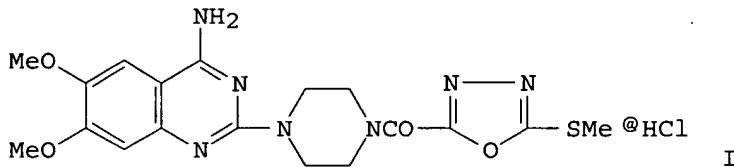
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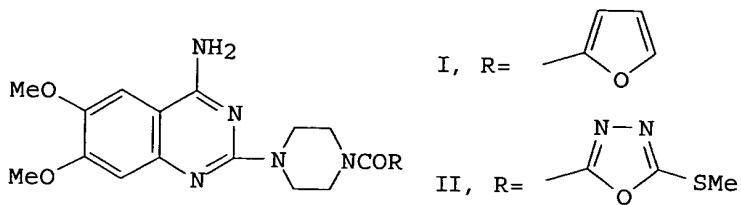
- AB The effects on blood pressure and heart rate of prazosin and a structurally-related congener, BL-5111A (I) [62412-39-9], were compared in conscious and anesthetized rats. Both agents induced dose-related falls in systolic and diastolic blood pressure, with relatively little effect on heart rate. The hypotensive potency of prazosin was twenty-fold greater than that of I. The hypotensive activity of prazosin was abolished by pretreatment with the ganglionic blocking agent, pentolinium, or the α -adrenoceptor blocking agent, phentolamine, whereas I retained significant hypotensive activity (up to 28%) after either pretreatment. Both prazosin and I attenuated pressor responses to noradrenaline, and reversed the responses to adrenaline, prazosin being, in this respect, 6 times more potent than I. There was a highly significant relationship between the α -adrenoceptor blocking activity of either agent and its hypotensive effect. I differed from prazosin in possessing, in addition to its predominant α -adrenoceptor blocking action, a minor component of action attributable to direct vasodilatation.

L61 ANSWER 76 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1980:51901 HCAPLUS
 DOCUMENT NUMBER: 92:51901
 TITLE: A new prazosin analog BL-5111A
 AUTHOR(S): Oates, H. F.; Stoker, L. M.
 CORPORATE SOURCE: Kanematsu Mem. Inst., Sydney Hosp., Sydney, 2000,
 Australia
 SOURCE: Archives Internationales de Pharmacodynamie et de
 Therapie (1979), 240(2), 305-13
 CODEN: AIPTAK; ISSN: 0003-9780
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The effects on blood pressure and heart rate of the antihypertensive agent, prazosin, were compared in anesthetized rats with those of a new structurally-related congener, BL-5111A n(I) [62412-39-9]. Both agents, administered i.v., induced dose-related falls in systolic and diastolic blood pressure, unaccompanied by compensatory tachycardia. The hypotensive efficacy of I was equal to that of prazosin, but its potency on a weight basis was considerably less. The hypotensive activity of prazosin was totally abolished after either ganglionic or α -adrenoceptor blockade, whereas I retained 17-28% of its activity after either pretreatment. Prazosin (0.1 mg/kg) and I (0.5 mg/kg) were equally effective in antagonizing pressor responses to noradrenaline, and in causing reversal of responses to adrenaline, whereas responsiveness to angiotensin II was either enhanced or unchanged. I, like prazosin, could be readily extracted from plasma and quantified by spectrofluorimetric assay. Thus I is an effective hypotensive agent, which differs from prazosin in possessing, in addition to its predominant α -adrenoceptor blocking action, a small component of action attributable to a direct vasodilator effect.

L61 ANSWER 77 OF 77 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1979:132852 HCAPLUS
 DOCUMENT NUMBER: 90:132852
 TITLE: Comparative first dose effects of prazosin and tiiodazosin (BL-5111) in spontaneously hypertensive rats
 AUTHOR(S): Roebel, L. E.; Florczyk, A. P.; Buyniski, J. P.
 CORPORATE SOURCE: Bristol Lab., Bristol-Myers Co., Syracuse, NY, USA
 SOURCE: Research Communications in Chemical Pathology and Pharmacology (1979), 23(1), 29-35
 CODEN: RCOCB8; ISSN: 0034-5164
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



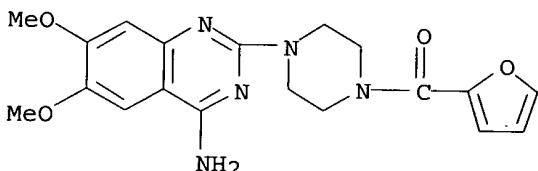
AB Prazosin (I) [19216-56-9] produces a first-dose phenomenon in man characterized by an exaggerated hypotensive response to the initial dose of the drug, with subsequent doses not producing this exaggerated effect. In spontaneously hypertensive rats (SHR), I (1 mg/kg, orally) produced a similar effect, appreciably reducing systolic blood pressure at 12 h after the first dose but having little or no effect at 12 h after subsequent doses. In contrast, BL-5111 (II) [66969-81-1] had no effect on blood pressure at 12 h after dosing (1 and 2 mg/kg). Pretreatment of rats with an ineffective blood pressure-lowering dose of I (0.03 mg/kg) attenuated the first dose effect of I, resembling the clin. effects in patients. Thus, the SHR may be a useful model for predicting the I-like first-dose phenomenon with related analogs.

IT 19216-56-9 66969-81-1

RL: BIOL (Biological study)
(blood pressure response to, in hypertension)

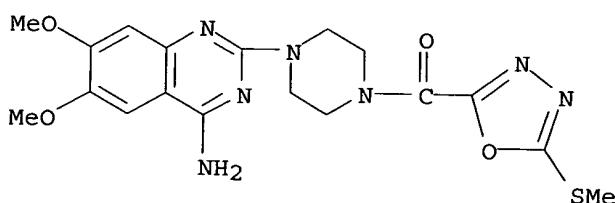
RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)- (9CI) (CA INDEX NAME)



RN 66969-81-1 HCPLUS

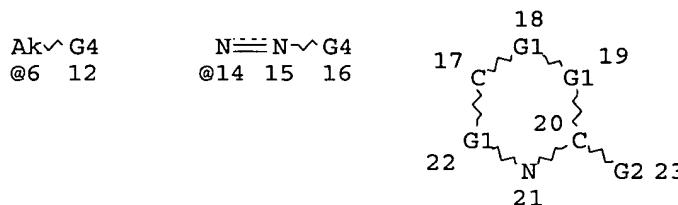
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[5-(methylthio)-1,3,4-oxadiazol-2-yl]carbonyl- (9CI) (CA INDEX NAME)



=> => d stat que 169

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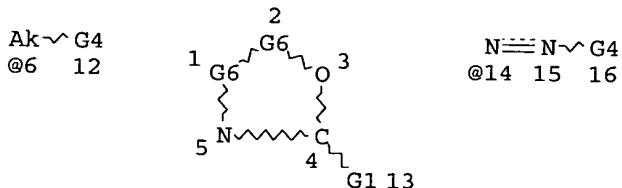
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STEREO ATTRIBUTES: NONE

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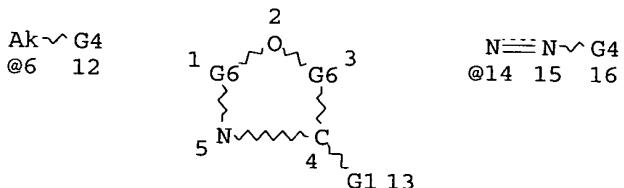
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NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE

L38 STR



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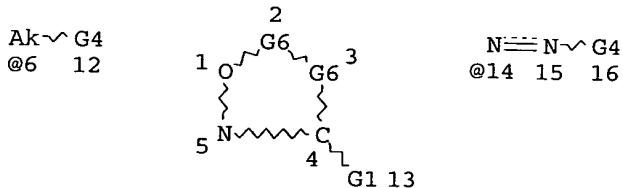
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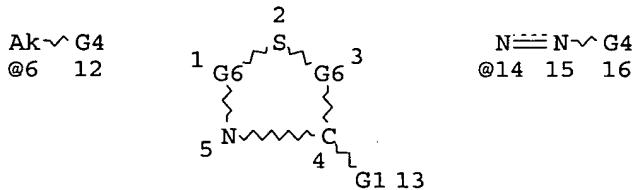
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NUMBER OF NODES IS 11

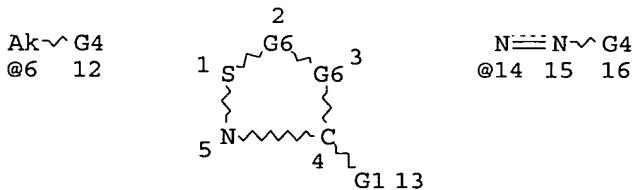
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GRAPH ATTRIBUTES:
RSPEC 4
NUMBER OF NODES IS 11

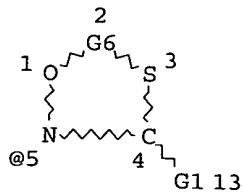
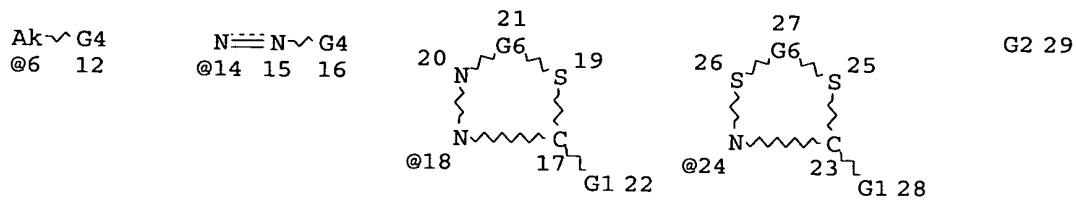
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DEFAULT MLEVEL IS ATOM
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GRAPH ATTRIBUTES:
RSPEC 4
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
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NUMBER OF NODES IS 24
  
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=> d ibib abs hitstr 169

L69 ANSWER 1 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2006:382064 HCPLUS
 TITLE: Effect of cyclooxygenase inhibitors on the micturition reflex in rats: correlation with inhibition of cyclooxygenase isozymes
 AUTHOR(S): Angelico, Patrizia; Guarneri, Luciano; Velasco, Cristina; Cova, Rita; Leonardi, Amedeo; Clarke, David E.; Testa, Rodolfo
 CORPORATE SOURCE: Pharmaceutical R & D Division, Recordati SpA, Milan, Italy
 SOURCE: BJU International (2006), 97(4), 837-846
 CODEN: BJINFO; ISSN: 1464-4096
 PUBLISHER: Blackwell Publishing Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB OBJECTIVE To investigate the role of cyclooxygenase (COX) isoenzymes (COX-1 and -2) in the regulation of bladder volume capacity (BVC) in several rat urodynamic models, using a selection of nonsteroidal anti-inflammatory drugs (NSAIDs), some selective for COX-2, correlating the potency of the tested compds. in the urodynamic models and their in vitro potency as inhibitors of COX isoenzymes, to verify the relative importance of the different isoenzymes. MATERIALS AND METHODS The effects of an i.v. administration of several nonselective and selective COX-2 inhibitors (indomethacin, meloxicam, naproxen, aspirin, paracetamol, flurbiprofen, nimesulide, NS-398, celecoxib, rofecoxib and L 745337) on bladder filling and voiding were evaluated in conscious and anesthetized rats by cystometry. The cystometry was done in conscious rats 1 day after catheter implantation, by filling the bladder with dilute acetic acid (0.2%) or saline, and again with saline 5 days after catheterization. Effects on isovolumic bladder contractions in anesthetized rats were also evaluated. RESULTS All the NSAIDs tested dose-dependently increased BVC; their potency at increasing BVC during infusion of the bladder with acetic acid was similar to that evaluated with saline on cystometry 1 day after catheterization. When a nonselective (naproxen) and a selective (nimesulide) COX-2 inhibitor were tested in rats with bladders infused with saline 5 days after catheterization, their effects on BVC were significantly lower than those evaluated at 1 day. All tested compds. dose-dependently inhibited isovolumic bladder contractions in anesthetized rats. There was a good correlation between the potency in inhibiting the isovolumic bladder contractions in anesthetized rats and in increasing BVC during cystometry in conscious rats with the bladder infused with acetic acid. The potency of the compds. in the cystometry model with bladders infused with acetic acid and in the isovolumic bladder voiding contractions correlated well with COX-2 inhibition, but not COX-1. CONCLUSIONS Both nonselective and COX-2 selective inhibitors are more active in inhibiting the micturition reflex in rats with bladder overactivity caused by bladder irritation than in normal rats. The potency of the anti-inflammatory compds. in inhibiting bladder overactivity induced by chemical or surgical irritation, and their activity in a cystometrog. model practically independent of bladder irritation (isovolumic bladder contractions in anesthetized rats), was related to the potency as inhibitors of COX-2 isoenzyme. This suggests that the involvement of prostaglandins in the micturition reflex in rats is mainly mediated by this isoenzyme.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 169 2-75

L69 ANSWER 2 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1214944 HCAPLUS
DOCUMENT NUMBER: 144:16813
TITLE: Urodynamic effects of oxybutynin and tolterodine in conscious and anesthetized rats under different cystometrographic conditions
AUTHOR(S): Angelico, Patrizia; Velasco, Cristina; Guarneri, Luciano; Sironi, Giorgio; Leonardi, Amedeo; Testa, Rodolfo
CORPORATE SOURCE: Pharmaceutical R and D Division, Recordati S.p.A., Milan, 20148, Italy
SOURCE: BMC Pharmacology (2005), 5, No pp. given
CODEN: BPMHEU; ISSN: 1471-2210
URL: <http://www.biomedcentral.com/content/pdf/1471-2210-5-14.pdf>
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Antimuscarinic agents are the most popular treatment for overactive bladder and their efficacy in man is well documented, producing decreased urinary frequency and an increase in bladder capacity. During cystometry in rats, however, the main effect reported after acute treatment with antimuscarinics is a decrease in peak micturition pressure together with little or no effect on bladder capacity. In the present expts. we studied the effects, in rats, of the two most widely used antimuscarinic drugs, namely oxybutynin and tolterodine, utilizing several different cystometrog. conditions. The aim was to determine the exptl. conditions required to reproduce the clin. pharmacol. effects of antimuscarinic agents, as seen in humans, in particular their ability to increase bladder capacity. I.v. or oral administration of tolterodine or oxybutynin in conscious rats utilized 1 day after catheter implantation and with saline infusion at constant rate of 0.1 mL/min, gave a dose-dependent decrease of micturition pressure (MP) with no significant change in bladder volume capacity (BVC). When the saline infusion rate into the bladder was decreased to 0.025 mL/min, the effect of oral oxybutynin was similar to that obtained with the higher infusion rate. Also, expts. were performed in rats in which bladders were infused with suramin (3 and 10 μ M) in order to block the non-adrenergic, non-cholinergic component of bladder contraction. Under these conditions, oral administration of oxybutynin significantly reduced MP (as observed previously), but again BVC was not significantly changed. In conscious rats with bladders infused with diluted acetic acid, both tolterodine and oxybutynin administered at the same doses as in animals infused with saline, reduced MP, although the reduction appeared less marked, with no effect on BVC. In conscious rats utilized 5 days after catheter implantation, a situation where inflammation due to surgery is reduced, the effect of tolterodine (i.v.) and oxybutynin (p.o.) on MP was smaller and similar, resp., to that observed in rats utilized 1 day after catheter implantation, but the increase of BVC was not statistically significant. In anesthetized rats, i.v. administration of oxybutynin again induced a significant decrease in MP, although it was of questionable relevance. Both BVC and threshold pressure were not significantly reduced. The number and amplitude of high frequency oscillations in MP were unmodified by treatment. Finally, in conscious

obstructed rats, i.v. oxybutynin did not modify frequency and amplitude of non-voiding contractions or bladder capacity and micturition volume Conclusion Despite the different exptl. conditions used, the only effect on cystometrogr. parameters of oxybutynin and tolterodine in anesthetized and conscious rats was a decrease in MP, whereas BVC was hardly and non-significantly affected. Therefore, it is difficult to reproduce in rats the cystometrogr. increase in BVC as observed in humans after chronic administration of antimuscarinic agents, whereas the acute effects seem more similar.

IT 5633-20-5, Oxybutynin 124937-51-5,

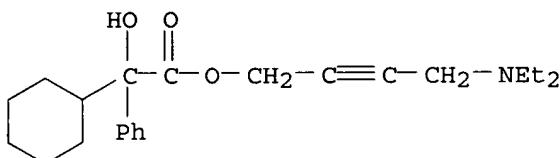
Tolterodine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(urodynamic effects of oxybutynin and tolterodine
in conscious and anesthetized rats under different cystometrogr.
conditions)

RN 5633-20-5 HCAPLUS

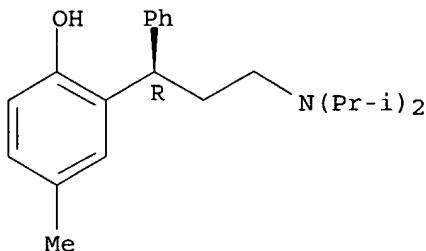
CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
4-(diethylamino)-2-butyanyl ester (9CI) (CA INDEX NAME)



RN 124937-51-5 HCAPLUS

CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 3 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:672881 HCAPLUS

DOCUMENT NUMBER: 143:146731

TITLE: Combination therapy with 5-HT1A and 5-HT1B receptor antagonists for treatment of neuromuscular dysfunction of the lower urinary tract

INVENTOR(S): Leonardi, Amedeo; Guarneri, Luciano; Testa, Rodolfo

PATENT ASSIGNEE(S): Recordati Ireland Ltd., Ire.

SOURCE: U.S. Pat. Appl. Publ., 41 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

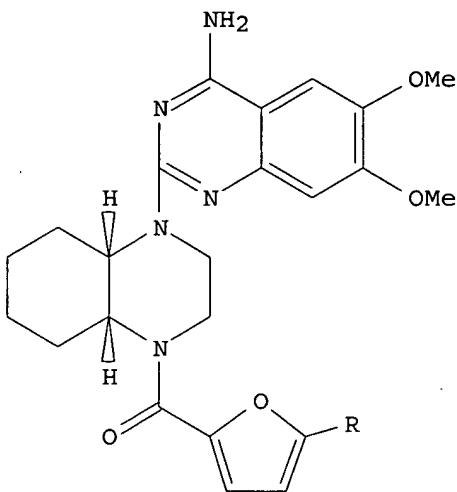
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005165025	A1	20050728	US 2005-41086	20050121
WO 2005070460	A2	20050804	WO 2005-EP719	20050124
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PRIORITY APPLN. INFO.: US 2004-538738P P 20040122
 OTHER SOURCE(S): MARPAT 143:146731

AB The invention describes the use of combinations of mols. endowed with antagonistic activity toward the serotonin 5-HT1A or 5-HT1B receptor, and of mols. simultaneously endowed with antagonistic activity at both receptors. These compds. and their enantiomers, diastereoisomers, N-oxides, polymorphs, solvates, prodrugs, and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract. Also described are pharmaceutical compns. containing them. Also provided is a method of therapeutic treatment of urinary disorders in a mammal, including a human, comprising administering to the mammal, including human, in need of such treatment, a therapeutically effective amount of a composition according to the invention.

L69 ANSWER 4 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:461126 HCPLUS
 DOCUMENT NUMBER: 143:71006
 TITLE: Non-competitive inhibitors of metabotropic glutamate receptor 5 (mGluR5)
 AUTHOR(S): Tasler, Stefan; Kraus, Juergen; Pegoraro, Stefano;
 Aschenbrenner, Andrea; Poggesi, Elena;
 Testa, Rodolfo; Motta, Gianni; Leonardi, Amedeo
 CORPORATE SOURCE: 4SC AG, Am Klopferspitz 19a, Martinsried, 82152, Germany
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(11), 2876-2880
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier B.V.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Based on a pharmacophore alignment on known noncompetitive mGluR5 inhibitors applying 4SCan technol., a new lead series was identified and further structurally investigated. Ki's as low as around 100 nM were achieved.
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2004:1001435 HCPLUS
 DOCUMENT NUMBER: 142:211400
 TITLE: (+)-Cyclazosin derivatives as α 1-adrenoceptor antagonists
 AUTHOR(S): Sagratini, Gianni; Buccioni, Michela; Gulini, Ugo;
 Marucci, Gabriella; Melchiorre, Carlo; Leonardi, Amedeo; Testa, Rodolfo; Giardina, Dario
 CORPORATE SOURCE: Department of Chemical Sciences, University of Camerino, Camerino, Italy
 SOURCE: Medicinal Chemistry Research (2004), 13(3/4), 190-199
 CODEN: MCREEB; ISSN: 1054-2523
 PUBLISHER: Birkhaeuser Boston
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The prazosin-related compound (+)-cyclazosin [(+)-1 (I; R = H)] is an α 1-adrenoceptor antagonist with moderate selectivity for the α 1b-adrenoceptor subtype (selectivity ratio: α 1b/ α 1a = 90, α 1b/ α 1d = 24). To improve its pharmacol. profile, the novel chiral derivs. (+)-2-(+)-5, bearing a bromo, a Me, a methoxy or an acetyl group in position 5 of the 2-furoyl moiety, were synthesized and evaluated for their α 1-adrenoceptor blocking activity. All the compds. displayed, like (+)-1, high and preferential affinity for the α 1b-adrenoceptor in binding and functional assays. Interestingly, in functional assays, compds. (+)-3 (I; R = ME) and (+)-4 (I; R = OMe) showed, in comparison with (+)-1, an increase in the α 1B/ α 1A selectivity (407 and 724 vs. 44), whereas compound (+)-5 exhibited an improved α 1B/ α 1D selectivity (1513 vs. 138).

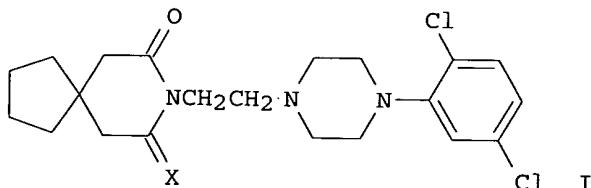
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 6 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:1001430 HCPLUS
 DOCUMENT NUMBER: 142:16952
 TITLE: Cardiovascular and urinary system receptors:
 Focus on endothelin receptor and α 1-adrenoceptor subtypes

AUTHOR(S): Testa, Rodolfo; Leonardi, Amedeo
 CORPORATE SOURCE: Pharmaceutical R and D Division-Recordati S.p.A., Milan, Italy
 SOURCE: Medicinal Chemistry Research (2004), 13(3/4), 131-133
 CODEN: MCREEB; ISSN: 1054-2523
 PUBLISHER: Birkhaeuser Boston
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. Specific topics discussed were: endothelin receptor subtypes in the cardiovascular system and α_1 adrenoceptor subtypes in the urinary system. Both the physiol and therapeutical implications of the receptor systems are discussed.
 REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 7 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:199199 HCPLUS
 DOCUMENT NUMBER: 140:406783
 TITLE: Synthesis, Screening, and Molecular Modeling of New Potent and Selective Antagonists at the α_{1d} Adrenergic Receptor
 AUTHOR(S): Leonardi, Amedeo; Barlocchio, Daniela; Montesano, Federica; Cignarella, Giorgio; Motta, Gianni; Testa, Rodolfo; Poggesi, Elena; Seeber, Michele; De Benedetti, Pier G.; Fanelli, Francesca
 CORPORATE SOURCE: Pharmaceutical R D Division, Recordati s.p.a., Milan, 20148, Italy
 SOURCE: Journal of Medicinal Chemistry (2004), 47(8), 1900-1918
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 140:406783
 GI



AB More than 75 compds. structurally related to BMY 7378 have been designed and synthesized. Structural variations of each part of the reference mol. have been introduced, obtaining highly selective ligands for the α_{1d} adrenergic receptor. The mol. determinants for selectivity at this receptor are essentially held by the Ph substituent in the phenylpiperazine moiety. The integration of an extensive SAR anal. with docking simulations using the rhodopsin-based models of the three α_1 -AR subtypes and of the 5-HT1A receptor provides significant insights into the characterization of the receptor binding sites as well as into the mol. determinants of ligand selectivity at the α_{1d} -AR and the 5-HT1A receptors. The results of multiple copies simultaneous search (MCSS) on the substituted phenylpiperazines together with those of

manual docking of compds. BMY 7378 and 69 into the putative binding sites of the α 1A-AR, α 1B-AR, α 1D-AR, and the 5-HT1A receptors suggest that the phenylpiperazine moiety would dock into a site formed by amino acids in helixes 3, 4, 5, 6 and extracellular loop 2 (E2), whereas the spirocyclic ring of the ligand docks into a site formed by amino acids of helixes 1, 2, 3, and 7. This docking mode is consistent with the SAR data produced in this work. Furthermore, the binding site of the imide moiety does not allow for the simultaneous involvement of the two carbonyl oxygen atoms in H-bonding interactions, consistent with the SAR data, in particular with the results obtained with the lactam derivative I [X = H₂]. The results of docking simulations also suggest that the second and third extracellular loops may act as selectivity filters for the substituted phenylpiperazines. The most potent and selective compds. for α 1D adrenergic receptor, i.e., I [X = O, H₂] are characterized by the presence of the 2,5-dichlorophenylpiperazine moiety.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 8 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:1006971 HCPLUS

DOCUMENT NUMBER: 140:59660

TITLE: Preparation of disubstituted diazacycloalkanes as serotonin 5-HT1A ligands for treatment of neuromuscular dysfunction of the lower urinary tract.

INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo

PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.

SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIIXD2

DOCUMENT TYPE: Patent

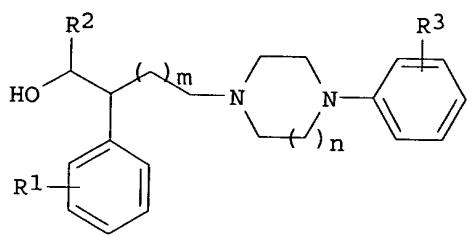
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003106444	A1	20031224	WO 2003-EP6280	20030616
WO 2003106444	C1	20040812		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2489450	AA	20031224	CA 2003-2489450	20030616
AU 2003276979	A1	20031231	AU 2003-276979	20030616
US 2004072822	A1	20040415	US 2003-463222	20030616
US 7071197	B2	20060704		
BR 2003011805	A	20050315	BR 2003-11805	20030616
EP 1515961	A1	20050323	EP 2003-740249	20030616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1662516	A	20050831	CN 2003-814264	20030616
JP 2005538063	T2	20051215	JP 2004-513276	20030616

NO 2005000146 US 2006148821 PRIORITY APPLN. INFO.:	A 20050314 A1 20060706	NO 2005-146 US 2006-364653 IT 2002-MI1328 US 2002-509038P US 2003-463222 WO 2003-EP6280	20050111 20060227 A 20020614 P 20020614 A1 20030616 W 20030616
OTHER SOURCE(S) : GI	MARPAT 140:59660		



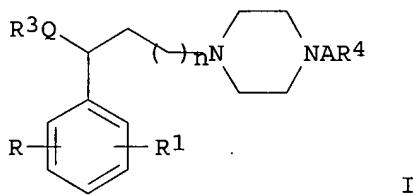
AB Title compds. I; [R1 = halo; R2 = C3-8 cycloalkyl; R3 = C1-4 alkoxy, haloalkoxy; m, n = 1, 2], were prepared for treatment of urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance (decreased bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder. I and their enantiomers, diastereoisomers, N-oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT1A receptor. Thus, 4-cyclohexyl-4-oxo-3-(2-fluorophenyl)butyraldehyde (preparation given), 1-(2-methoxyphenyl)piperazine HCl, Na triacetoxyborohydride and CH2Cl2 were stirred together at r.t. for 1 h and kept overnight to give 1-[4-cyclohexyl-4-oxo-3-(2-fluorophenyl)butyl]-4-(2-methoxyphenyl)piperazine. The latter was stirred with NaBH4 in MeOH to give (SR,RS)- and (RR,SS)-1-cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-(2-fluorophenyl)butan-1-ol. The (SR,RS)-diastereomer bound to 5-HT1A receptors with Ki = 0.13 nM.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 9 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:1006970 HCPLUS
 DOCUMENT NUMBER: 140:42211
 TITLE: Preparation of phenylalkylpiperazines for treatment of diseases related to 5-HT1A receptor activity.
 INVENTOR(S): Leonardi, Amadeo; Motta, Gianni; Riva, Carlo; Poggesi, Elena
 PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.
 SOURCE: PCT Int. Appl., 106 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003106443	A1	20031224	WO 2003-EP6289	20030616
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2489449	AA	20031224	CA 2003-2489449	20030616
AU 2003246434	A1	20031231	AU 2003-246434	20030616
US 2004072839	A1	20040415	US 2003-463196	20030616
BR 2003011804	A	20050329	BR 2003-11804	20030616
EP 1549627	A1	20050706	EP 2003-759960	20030616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006502102	T2	20060119	JP 2004-513275	20030616
NZ 537470	A	20060630	NZ 2003-537470	20030616
NO 2005000147	A	20050314	NO 2005-147	20050111
PRIORITY APPLN. INFO.:			IT 2002-MI1327	A 20020614
			US 2002-505350P	P 20020614
			WO 2003-EP6289	W 20030616

OTHER SOURCE(S): MARPAT 140:42211
GI



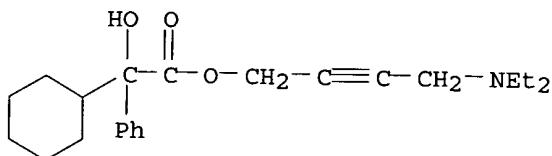
- AB Title compds. [I; R = H, halo, alkyl, alkoxy, alkylthio, OH, alkenyl, alkynyl, haloalkyl, aminoalkyl, cyano, alkylsulfonyl, dialkylaminosulfonyl, etc.; R1 = H, (R-substituted) cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heterocyclyloxy, heterocycloalkyl, heterocycloalkoxy; Q = CO, CH(OH), CH(OR2); R2 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl; R3 = H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl; R4 = (R-substituted) aryl, heterocyclyl; n = 1, 2; A = bond, CH2, CH2CH2], were prepared for treatment of CNS disorders, for reducing the frequency of bladder contractions, and for treating neuromuscular dysfunction of the lower urinary tract. Thus, 4-cyclohexyl-3-(2-fluorophenyl)-4-methoxybutyraldehyde (preparation given), 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine hydrochloride, Na triacetoxyborohydride, AcOH and CH2Cl2 were stirred together at room temperature for 1h, and kept overnight to give 1-[4-cyclohexyl-3-(2-fluorophenyl)-4-methoxybutyl]-4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine. The latter bound to 5-HT1A receptors with Ki = 1.45 nM.
- IT 5633-20-5, Oxybutynin 19216-56-9,
Prazosin 63590-64-7, Terazosin

74191-85-8, Doxazosin 81403-80-7,
 Alfuzosin 106133-20-4, Tamsulosin
 124937-51-5, Tolterodine 173324-94-2,
 Temiverine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (coadministration; preparation of phenylalkylpiperazines for treatment of
 diseases related to 5-HT1A receptor activity)

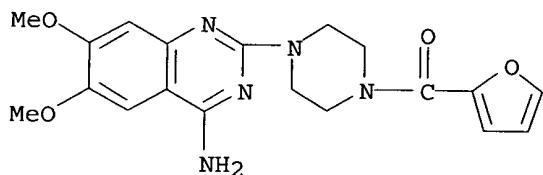
RN 5633-20-5 HCAPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



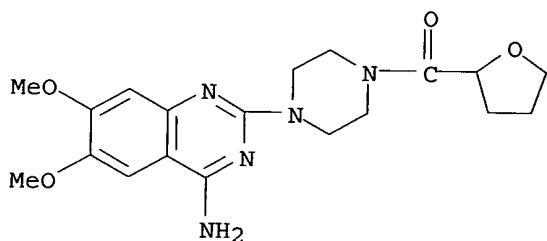
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-
 (9CI) (CA INDEX NAME)



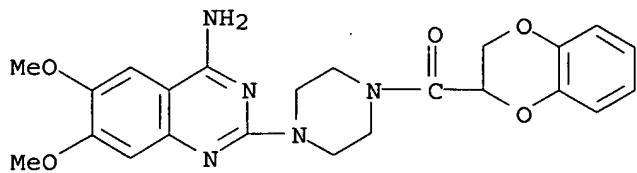
RN 63590-64-7 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



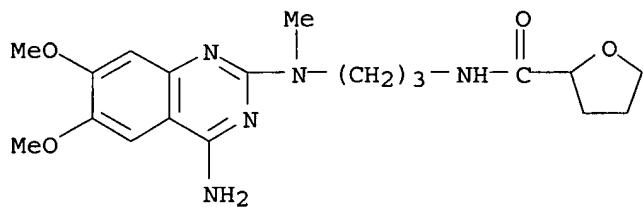
RN 74191-85-8 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



RN 81403-80-7 HCAPLUS

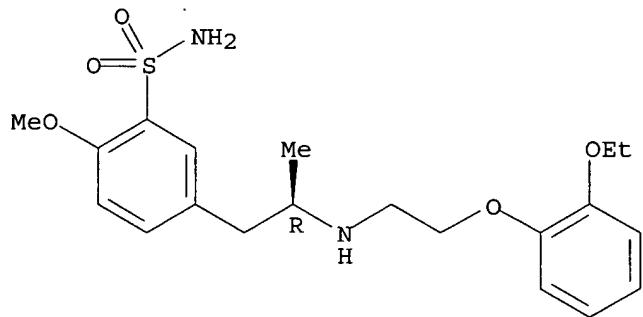
CN 2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

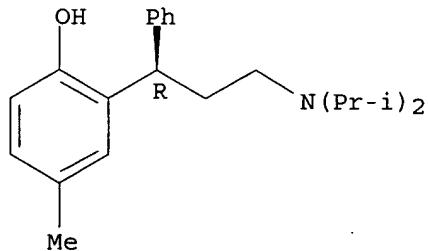
Absolute stereochemistry. Rotation (-).



RN 124937-51-5 HCAPLUS

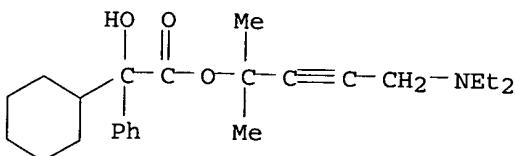
CN Phenol, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173324-94-2 HCAPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-,
4-(diethylamino)-1,1-dimethyl-2-butynyl ester (9CI) (CA INDEX NAME)



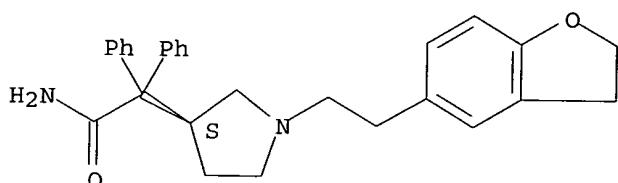
IT 133099-04-4, Darifenacin

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of phenylalkylpiperazines for treatment of diseases related to
5-HT1A receptor activity)

RN 133099-04-4 HCAPLUS

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-
 α,α -diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 10 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:799341 HCAPLUS

DOCUMENT NUMBER: 139:395795

TITLE: Prazosin-Related Compounds. Effect of Transforming the Piperazinylquinazoline Moiety into an Aminomethyltetrahydroacridine System on the Affinity for α 1-Adrenoreceptors

AUTHOR(S): Rosini, Michela; Antonello, Alessandra; Cavalli, Andrea; Bolognesi, Maria L.; Minarini, Anna; Marucci, Gabriella; Poggesi, Elena; Leonardi, Amedeo; Melchiorre, Carlo

CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Bologna, Bologna, 40126, Italy

SOURCE: Journal of Medicinal Chemistry (2003), 46(23), 4895-4903

PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623 American Chemical Society

DOCUMENT TYPE: Journal

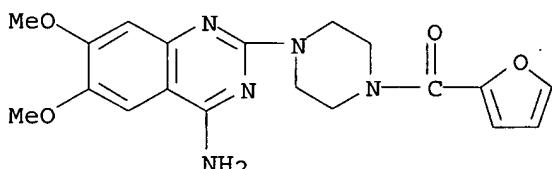
LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:395795

AB In a search for structurally new α 1-adrenoreceptor (α 1-AR) antagonists, prazosin-related compds. were synthesized and their affinity profiles were assessed by functional expts. in isolated rat vas deferens (α 1A), spleen (α 1B), and aorta (α 1D) and by binding assays in CHO cells expressing human cloned α 1-AR subtypes. Transformation of the piperazinylquinazoline moiety of prazosin

into an aminomethyltetrahydroacridine system afforded N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-2-furancarboxamide, endowed with reduced affinity, in particular for the α 1A-AR subtype. Then, to investigate the optimal features of the tricyclic moiety, the aliphatic ring of N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-2-furancarboxamide was modified by synthesizing the lower and higher homologs, N-[(9-amino-2,3-dihydro-6,7-dimethoxy-1H-cyclopenta[b]quinolin-2-yl)methyl]-2-furancarboxamide hydrochloride and N-[(11-amino-7,8,9,1-tetrahydro-2,3-dimethoxy-6H-cyclopenta[b]quinolin-7-yl)methyl]-2-furancarboxamide hydrochloride. An anal. of the pharmacol. profile, together with a mol. modeling study, indicated the tetrahydroacridine moiety as the most promising skeleton for α 1-antagonism. N-[(9-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]benzamide hydrochloride, N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-2-(trifluoromethyl)benzamide hydrochloride, etc., where the replacement of the furoyl group of N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-2-furancarboxamide hydrochloride with a benzoyl moiety afforded the possibility to evaluate the effect of the substituent trifluoromethyl on receptor binding, resulted, except for N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride, in a rather surprising selectivity toward α 1B-AR, in particular vs the α 1A subtype. Also the insertion of the 2,6-dimethoxyphenoxyethyl function of WB 4101 on the tetrahydroacridine skeleton of N-[(9-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-3-acridinyl)methyl]-2-furancarboxamide hydrochloride, and/or the replacement of the aromatic amino function with a hydroxy group, resulted in α 1B-AR selectivity also vs the α 1D subtype. On the basis of these results, the tetrahydroacridine moiety emerged as a promising tool for the characterization of the α 1-AR, owing to the receptor subtype selectivity achieved by an appropriate modification of the lateral substituents.

- IT 19216-56-9DP, Prazosin, analogs and derivs.
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of prazosin-related compds. and effect of transforming piperazinylquinazoline moiety into (aminomethyl)tetrahydroacridine system on the affinity for α 1-adrenoreceptors)
- RN 19216-56-9 HCPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 11 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:625558 HCPLUS
 DOCUMENT NUMBER: 140:70835
 TITLE: Effects of intravenous and infravesical administration of suramin, terazosin and BMY 7378 on bladder instability in conscious rats with

AUTHOR(S) : bladder outlet obstruction
 Velasco, C.; Guarneri, L.; Leonardi, A.;
 Testa, R.

CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati SpA, Milan,
 Italy

SOURCE: BJU International (2003), 92(1), 131-136
 CODEN: BJINFO; ISSN: 1464-4096

PUBLISHER: Blackwell Publishing Ltd.

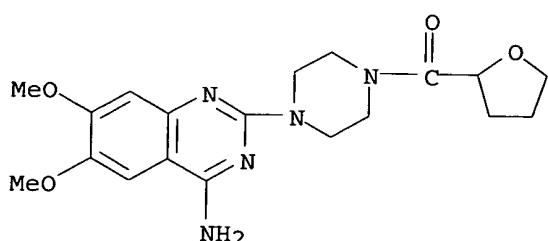
DOCUMENT TYPE: Journal

LANGUAGE: English

AB To evaluate the effect of the nonselective purinergic antagonist suramin and the α_1 -adrenergic antagonists, terazosin and BMY 7378, given i.v. or infused directly into the bladder during cystometry in conscious rats with bladder outlet obstruction induced by urethral ligation. Cystometry was performed in conscious female rats recording bladder volume capacity (BVC), evaluated as the amount of saline infused between two voiding cycles, and micturition volume (MV). Changes in frequency and amplitude of spontaneous non-voiding bladder contractions (NVC) were also recorded. The effects of the i.v. administration of suramin (100 mg/kg), BMY 7378 (1 mg/kg), and terazosin (0.3 mg/kg) on NVC, BVC and MV were evaluated in obstructed rats with bladder infusion of saline. The effects of infravesical infusion of suramin (3-10 μ mol/L), terazosin (1 μ mol/L) and BMY 7378 (10 μ mol/L) were also evaluated and compared with values observed in control rats during saline infusion into the bladder. I.v. injection with suramin had no effects on NVC, BVC and MV, but suramin infused into the bladder induced a consistent reduction in the amplitude of NVC (significantly different from matched control animals) with a tendency to reduce their frequency. BVC and MV were slightly but significantly decreased by infravesical infusion of suramin. In contrast, BMY 7378 and terazosin, given i.v., were extremely potent at inhibiting the frequency and amplitude of the NVC, but were inactive on NVC when infused into bladder. These findings confirm a role for α_1 -adrenergic receptors in bladder instability caused by bladder outlet obstruction. In addition, a purinergic neurotransmitter, presumably ATP, is shown to be involved.

IT 63590-64-7, Terazosin
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (effects of i.v. and infravesical administration of suramin, terazosin and BMY 7378 on bladder instability in rats with bladder outlet obstruction)

RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



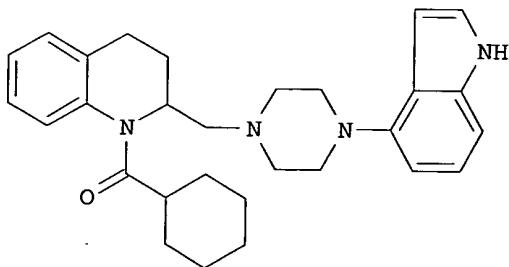
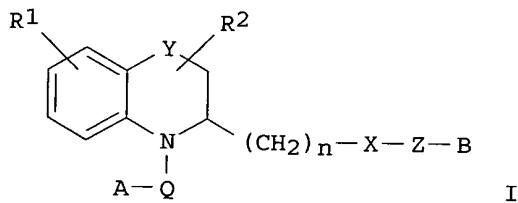
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 12 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:463127 HCPLUS
 DOCUMENT NUMBER: 140:174409
 TITLE: Searching for cyclazosin analogues as
 α 1B-adrenoceptor antagonists
 AUTHOR(S): Giardina, Dario; Polimanti, O.; Sagratini, G.; Angeli,
 P.; Gulini, U.; Marucci, G.; Melchiorre, C.;
 Poggesi, E.; Leonardi, A.
 CORPORATE SOURCE: Department of Chemical Sciences, University of
 Camerino, Camerino, I 62032, Italy
 SOURCE: Farmaco (2003), 58(7), 477-487
 CODEN: FRMCE8; ISSN: 0014-827X
 PUBLISHER: Editions Scientifiques et Medicales Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A series of quinazoline derivs., 2-20, structurally related to the racemic
 α 1-adrenoceptor antagonist cyclazosin (1), were synthesized and
evaluated for their functional antagonism at α 1- and
 α 2-adrenoceptors and for their binding affinity at human cloned
 α 1a-, α 1b- and α 1d-adrenoceptor subtypes. They
displayed, like 1, preferential antagonism and selectivity for α 1
vs. α 2-adrenoceptors. Compds. 10, 13, and 18 showed high potency at
 α 1-adrenoceptors similar to that of 1 (pKB values 8.47-8.89 vs.
8.67), whereas 13 and 15 were endowed with the highest
 α 1-adrenoceptor selectivity, only 3- to 4-fold lower than that of 1.
In binding expts., all of the compds. displayed an affinity practically
similar to that found for 1, with the exception of 19 and 20 that were
definitely less potent. The s-triazine analog 18 was the most potent of
the series with pKi values of 10.15 (α 1a), 10.22 (α 1b) and
10.40 (α 1d), resulting 77-fold more potent than 1 at
 α 1a-adrenoceptors. In addition, the majority of compds., like
prototype 1, showed the same trend of preferential affinity for α 1d-
and α 1b-adrenoceptors that α 1a-subtype. In conclusion, we
identified compds. 2-5, 10, 12 and 13, bearing either an aliphatic- or an
arylalkyl- or aryloxyalkyl-acyl function, with an interesting
subtype-selectivity profile, which makes them suitable candidates for
their resolution as enantiomers structurally related to (+)-cyclazosin.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 13 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2003:301077 HCPLUS
 DOCUMENT NUMBER: 138:304309
 TITLE: Preparation of 2-(heterocyclalkyl)-1,2,3,4-
tetrahydroquinolines and analogs as 5-HT1A receptor
inhibitors for treatment of urinary tract
disorders
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo;
Testa, Rodolfo; Corbett, Jeff W.
 PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica e
Farmaceutica S.p.A.
 SOURCE: PCT Int. Appl., 212 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031436	A1	20030417	WO 2002-EP11282	20021007
WO 2003031436	C1	20040527		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2458456	AA	20030417	CA 2002-2458456	20021007
US 2003162777	A1	20030828	US 2002-266104	20021007
US 2003181446	A1	20030925	US 2002-266088	20021007
EP 1432701	A1	20040630	EP 2002-782863	20021007
EP 1432701	B1	20051221		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
BR 2002013067	A	20040928	BR 2002-13067	20021007
CN 1564820	A	20050112	CN 2002-819728	20021007
JP 2005508952	T2	20050407	JP 2003-534419	20021007
NZ 532511	A	20051028	NZ 2002-532511	20021007
ES 2253568	T3	20060601	ES 2002-2782863	20021007
NO 2004001833	A	20040705	NO 2004-1833	20040504
ZA 2004003356	A	20041108	ZA 2004-3356	20040504
PRIORITY APPLN. INFO.:			IT 2001-MI2060	A 20011005
			US 2002-350680P	P 20020122
			WO 2002-EP11282	W 20021007
OTHER SOURCE(S)	NO PCT/EP 2002/00122			



AB Title compds. I [wherein R1 = H, halo, OH, (halo)alkyl, (halo)alkoxy, NO₂,

NR3R4, or (un)substituted Ph or heterocyclyl; R2 = 1 or 2 substituents selected from H or alkyl; R3 and R4 = independently H, alkyl, acyl, or alkoxy carbonyl; Y = a bond or CH2; Q = CO, CS, or SO2; A = (un)substituted (cyclo)alkyl, (cyclo)alkenyl, aryl, heterocyclyl, (di)alkylamino, arylamino, or arylalkylamino; n = 1 or 2; X = (un)substituted piperidinyl or piperazinyl; Z = a bond, O, S, CH2, CH2CH2, CO, CHO, OCH2, NH, NHCO, or NHCONHCH2; or ZB = 2,3-dihydrobenzo[1,4]dioxin-2-yl; B = (un)substituted monocyclic or bicyclic (hetero)aryl; with provisos; and enantiomers, diastereomers, N-oxides, crystalline forms, hydrates, solvates, or pharmaceutically acceptable salts thereof] were prepared as serotonergic receptor antagonists. For example, coupling of 2-chloromethylquinoline with 1-(4-indolyl)piperazine in the presence of DIPEA in DMF gave 1-(4-indolyl)-4-(quinolin-2-ylmethyl)piperazine (70%), which was hydrogenated using PtO2/AcOH/H2 to provide the tetrahydroquinoline derivative (76.5%). Amidation with cyclohexanecarbonyl chloride in the presence of TEA in CH2Cl2 afforded II (81%). The (+)- and (-)-enantiomers were separated via chiral column chromatog. II inhibited the human 5HT1A-serotonergic receptor in transfected HeLa cells with Ki of 3.3 nM, while (+)-II showed a binding affinity with Ki of 0.2 nM. Similarly, (+)-II proved more effective than II in suppressing the frequency of rhythmic bladder -voiding contractions in rats with ED50 values of 24 µg/kg and 64 µg/kg, resp. In addition, (+)-II exhibited significant and long-lasting post-synaptic 5-HT1A-receptor antagonist activity by suppressing forepaw treading induced by 8-OH-DPAT in rats with 100% inhibition after 0.5 h and 98% inhibition after 4 h of administration of a dose of 1 mg/kg p.o. By contrast, (-)-II showed only 19% inhibition after 0.5 h and 5% inhibition after 4 h of administration of a dose of 1 mg/kg p.o.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 14 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:965126 HCPLUS

DOCUMENT NUMBER: 138:39297

TITLE: Preparation of 1-(N-phenylalkylaminoalkyl)piperazines as 5-HT1A receptor antagonists for treatment of neuromuscular dysfunction of the lower urinary tract

INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo

PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company, Italy

SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. 6,399,614.

CODEN: USXXCO

DOCUMENT TYPE: Patent

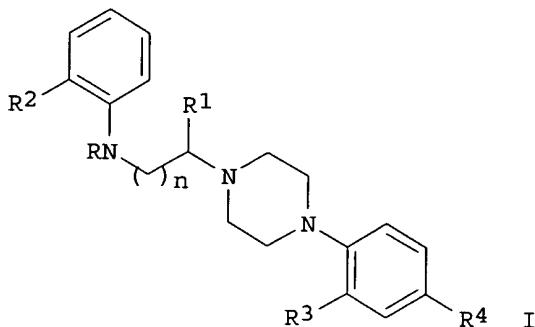
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002193383	A1	20021219	US 2002-132677	20020422
US 6071920	A	20000606	US 1998-127057	19980731
US 6399614	B1	20020604	US 2000-532505	20000321
PRIORITY APPLN. INFO.:			IT 1997-MI1864	A 19970801
			US 1997-70268P	P 19971231
			US 1998-127057	A2 19980731
			US 2000-532505	A2 20000321

OTHER SOURCE(S): MARPAT 138:39297
GI



AB Title compds. [I; R = H, alkylcarbonyl, cycloalkylcarbonyl, substituted cycloalkylcarbonyl, monocyclic heteroarylcarbonyl; R1 = H, alkyl; R2 = halo, alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulfonylamino, alkoxy carbonyl, N-acylaminocarbonyl, N-alkylaminocarbonyl, N,N-dialkylaminocarbonyl, aminocarbonyl, CF₃, polyfluoroalkoxy; R3 = methoxy, polyhaloalkoxy; R4 = H, OH, alkoxy, acyloxy, N-alkylaminocarbonyloxy N, N-dialkylaminocarbonyloxy; n = 1, 2], were prepared. Thus, N-(2-trifluoromethylphenyl)cyclohexanecarboxamide (preparation given), 1-(2-chloroethyl)-4-(2-methoxyphenyl)piperazine, 50% NaOH, TEBAC, and PhMe were stirred together at 80° for 3.5 h; addnl. N-(2-trifluoromethylphenyl)cyclohexanecarboxamide was then added followed by stirring at 80° for 6 h to give 1-[N-(2-trifluoromethylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)piperazine. The latter showed an ED₁₀ = 192 µg/kg for inhibiting bladder voiding contractions in rats.

L69 ANSWER 15 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:655085 HCAPLUS
 DOCUMENT NUMBER: 137:179926
 TITLE: Use of selective cyclooxygenase 2 (COX-2) inhibitors for the treatment of urinary incontinence
 INVENTOR(S): Leonardi, Amedeo; Testa, Rodolfo; Guarneri, Luciano
 PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company, Switz.
 SOURCE: U.S., 19 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6440963	B1	20020827	US 2001-969538	20011001
CA 2443031	AA	20021017	CA 2002-2443031	20020405
WO 2002080927	A1	20021017	WO 2002-EP3850	20020405
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1381369 A1 20040121 EP 2002-722290 20020405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
BR 2002008694 A 20040330 BR 2002-8694 20020405
JP 2004531514 T2 20041014 JP 2002-578966 20020405
CN 1688315 A 20051026 CN 2002-807810 20020405
ZA 2003007731 A 20040913 ZA 2003-7731 20031003
NO 2003004473 A 20031205 NO 2003-4473 20031006
PRIORITY APPLN. INFO.: IT 2001-MI733 A 20010405
WO 2002-EP3850 W 20020405

OTHER SOURCE(S): MARPAT 137:179926

AB The treatment of neuromuscular dysfunction of the lower urinary tract by compds. which selectively inhibit the COX-2 isoenzyme is described. The compds. concerned inhibit the COX-2 isoenzyme with a potency at least 10-fold, and preferably at least 100-fold, greater than their potency on the COX-1 isoenzyme.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 16 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:594729 HCPLUS

DOCUMENT NUMBER: 137:135118

TITLE: Selective α_1 - and α_2 adrenergic antagonists, their preparation, and their use in the treatment of lower urinary tract symptoms

INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Testa, Rodolfo

PATENT ASSIGNEE(S): Recordati Industria Chimica E Farmaceutica SPA, Italy; Recordati S.A. Chemical and Pharmaceutical Company

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060534	A2	20020808	WO 2002-EP950	20020130
WO 2002060534	A3	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002183290	A1	20021205	US 2002-60925	20020130
PRIORITY APPLN. INFO.:			IT 2001-MI164	A 20010130
			US 2001-311389P	P 20010810

OTHER SOURCE(S): MARPAT 137:135118

AB Described are derivs. with an adrenergic antagonistic activity and, in particular, high selectivity for α_1 and α_2 adrenergic receptors compared to α_1 -receptors. This selectivity

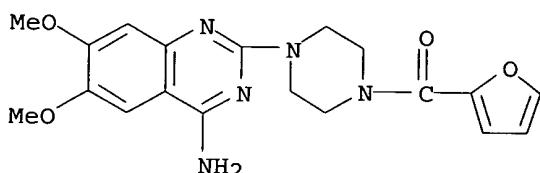
profile suggests use of these derivs. in the treatment of symptoms of the lower urinary tract, including those associated to benign prostatic hyperplasia, without the side effects associated to their hypotensive activity. Preparation of e.g. N-[3-(4-(2-methoxyphenyl)-1-piperazinyl)propyl]-7-keto-5-trifluoromethyl-7H-thieno[3,2-b]pyran-3-carboxamide is described.

IT 19216-56-9, Prazosin 63590-64-7,
Terazosin 106133-20-4, Tamsulosin

RL: PAC (Pharmacological activity); BIOL (Biological study)
(selective α_1 - and α_2 adrenergic
antagonist preparation and use for treatment of lower
urinary tract symptoms)

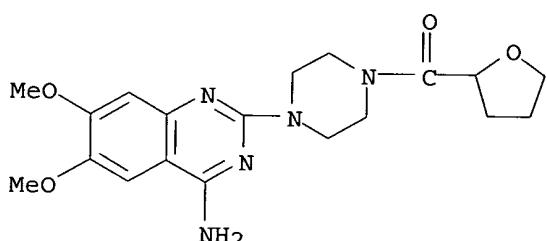
RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-
(9CI) (CA INDEX NAME)



RN 63590-64-7 HCAPLUS

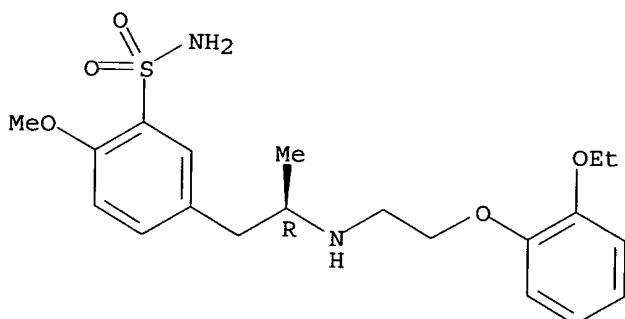
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

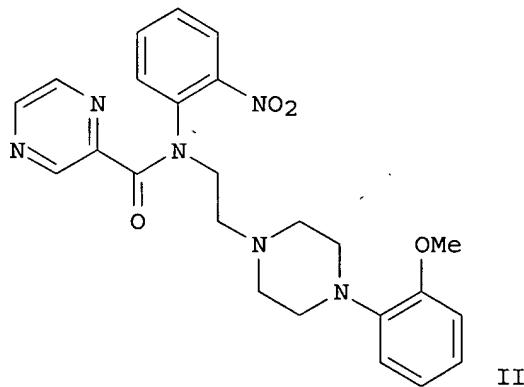
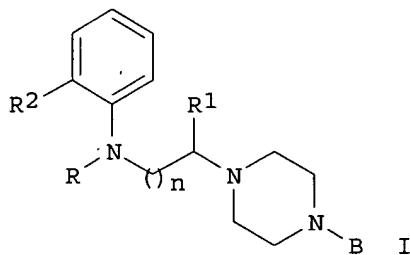
Absolute stereochemistry. Rotation (-).



L69 ANSWER 17 OF 75. HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2002:425416 HCPLUS
 DOCUMENT NUMBER: 137:6188
 TITLE: Preparation of substituted 1-(N-phenylaminoalkyl)piperazine derivatives as 5-HT1A receptor antagonists
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati S.A. Chemical and Pharmaceutical Company, Switz.
 SOURCE: U.S., 33 pp., Cont.-in-part of U. S. 6,071,920.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6399614	B1	20020604	US 2000-532505	20000321
US 6071920	A	20000606	US 1998-127057	19980731
US 2002193383	A1	20021219	US 2002-132677	20020422
PRIORITY APPLN. INFO.:			IT 1997-MI1864	A 19970801
			US 1997-70268P	P 19971231
			US 1998-127057	A2 19980731
			US 2000-532505	A2 20000321

OTHER SOURCE(S): MARPAT 137:6188
 GI



AB Title compds. I [R = H; R1 = H, alkyl; R2 = alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulfonylamino, alkoxy carbonyl, N-acylaminocarbonyl, N-alkylaminocarbonyl, N,N-di-alkylaminocarbonyl, aminocarbonyl, halo, trifluoromethyl, polyfluoroalkoxy; n = 1-2; B = aryl, bicyclic aryl, 9-member bicyclic heteroarom. containing one heteroatom, benzyl, with provisions] were prepared. For example, 2-chloronitrobenzene and 1-[2-aminoethyl]-4-[2-methoxyphenyl]piperazine were reacted (n-BuOH, K₂CO₃, reflux, 32 h) to give 1-[2-[N-[2-nitrophenyl]amino]ethyl]-4-[2-methoxyphenyl]piperazine. This intermediate was reacted with pyrazinecarbonyl chloride to afford II. II had Ki = 1.02 nM for the 5-HT1A receptor. I are contemplated for use in treating neuromuscular dysfunction of the lower urinary tract in a mammal.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 18 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:2007 HCPLUS

TITLE:

Influence of pump compliance (peristaltic vs. infusion) on urodynamic measurement during cystometry in conscious rats

AUTHOR(S):

Velasco, Cristina; Guarneri, Luciano; Leonardi, Amedeo; Testa, Rodolfo

CORPORATE SOURCE:

Pharmaceutical R & D Division-Recordati S.p.A., Milan, I-20148, Italy

SOURCE:

Journal of Pharmacological and Toxicological Methods (2001), 45(3), 215-221

CODEN: JPTMEZ; ISSN: 1056-8719

PUBLISHER:

Elsevier Science Inc.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB Cystometry, employing natural or pump-induced bladder filling, is the most widely used method for studying bladder reflexes and micturition in conscious rats. However, discrepancies in basal values of urodynamic parameters are often reported, especially for micturition pressure. The aim of this study was to establish whether the type of pump used (peristaltic or infusion) might yield different urodynamic parameters. Differences between natural filling (evaluated in water-loaded animals and considered "physiol. micturition") and pump-evoked cystometrograms, as well as the compliance of these systems, and the effects of pharmacol. diverse drugs (prazosin, oxybutynin, and naproxen) acting on the bladder voiding were evaluated. Micturition pressure recorded from pump-evoked cystometrograms showed differences from natural micturition that were related to the total compliance of the system (pump + tube) and not only to the nature of the pump used. Drug-induced changes of micturition pressure during natural micturition resembled those recorded during bladder infusion with a peristaltic pump more than those with an infusion pump. Other basal values and drug-induced changes of bladder capacity were the same during natural and pump-evoked micturition. The present findings indicate that cystometrog. parameters obtained during pump-evoked micturition with a system at high compliance (peristaltic pump) are equivalent to those observed during physiol. micturition.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 19 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:884762 HCPLUS

DOCUMENT NUMBER: 136:177854

TITLE: N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-

AUTHOR(S) : nitrophenyl)cyclohexanecarboxamide: a novel pre- and postsynaptic 5-hydroxytryptamine1A receptor antagonist active on the lower urinary tract
Leonardi, A.; Guarneri, L.; Poggesi, E.; Angelico, P.; Velasco, C.; Cilia, A.; Testa, R.

CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati S.p.A., Milan, Italy

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 299(3), 1027-1037
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-nitrophenyl)cyclohexanecarboxamide (Rec 15/3079) was synthesized with the aim of obtaining a novel compound with 5-hydroxytryptamine (5-HT)1A antagonistic properties and activity in controlling bladder function at the level of the central nervous system. Rec 15/3079 showed a selective high affinity for the 5-HT1A receptor ($K_i = 0.2$ nM). At the human recombinant 5-HT1A receptor, Rec 15/3079 acted as a competitive, neutral antagonist in that it did not modify basal [^{35}S]guanosine-5'-O-(3-thio)triphosphate binding to HeLa cell membranes but shifted the activation isotherm to 5-HT to the right, in a parallel manner, with a pK_b value of 10.5. Accordingly, Rec 15/3079 (i.v.) potently antagonized 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT)-induced hypothermia in mice ($ID_{50} = 36$ μ g/kg) and 8-OH-DPAT-induced forepaw treading in rats ($ID_{50} = 36$ μ g/kg). In vitro Rec 15/3079 was poorly active in antagonizing carbachol-induced bladder ($pD_2' = 5.03$) and norepinephrine-induced urethral (apparent $pK_b = 6$) contractions. However, in anesthetized rats, Rec 15/3079 (10-100 μ g/kg i.v.) blocked isovolemic bladder contractions with no effect on their amplitude. In conscious rats and guinea pigs with bladders filled with saline, Rec 15/3079 (300-1000 μ g/kg i.v.) increased bladder volume capacity (BVC) without affecting bladder contractility. In conscious rats with bladders filled with dilute acetic acid, Rec 15/3079 (300 μ g/kg i.v.) reversed the decrease of BVC induced by the acid. To evaluate apparent selective effect on lower urinary tract reflexes, Rec 15/3079 was tested in exptl. models for sedative, analgesic, anxiolytic, and antidepressant activity. Rec 15/3079 showed only a slight decrease in the duration of immobility in the behavioral despair test (antidepressant activity) at 1 mg/kg i.v. No anxiolytic activity was observed at 10 mg/kg i.v. No effect was observed in the hot plat test, but Rec 15/3079 increased tail-flick latencies after 3 to 10 mg/kg i.v. In conclusion, these studies demonstrate that Rec 15/3079 is endowed with favorable effects on bladder function, and it is devoid of unwanted side effects at the level of central nervous system at doses at least 10-fold higher than those active on the bladder. The treatment of incontinence with Rec 15/3079 is discussed.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 20 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:809680 HCAPLUS

DOCUMENT NUMBER: 136:85798

TITLE: trans-4-[4-(Methoxyphenyl)cyclohexyl]-1-arylpiperazines: A New Class of Potent and Selective 5-HT_{1A} Receptor Ligands as Conformationally Constrained Analogues of 4-[3-(5-Methoxy-1,2,3,4-

AUTHOR(S) : tetrahydronaphthalen-1-yl)propyl]-1-arylpiperazines
 Perrone, Roberto; Berardi, Francesco; Colabufo, Nicola
 A.; Leopoldo, Marcello; Lacivita, Enza; Tortorella,
 Vincenzo; Leonardi, Amedeo; Poggesi, Elena;
 Testa, Rodolfo

CORPORATE SOURCE: Dipartimento Farmaco-Chimico, Bari, 70126, Italy
 SOURCE: Journal of Medicinal Chemistry (2001), 44(25),
 4431-4442

PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623
 American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S) : CASREACT 136:85798

AB The influence of conformational parameters on the recognition by rat 5-HT1A receptors of derivs. of 4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]-1-(2-pyridinyl)piperazine (I) and 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N-[2-(2-pyridyloxy)ethyl]propanamine (II), two highly potent and selective 5-HT1A receptor ligands, is addressed. Fifteen flexible and rigid analogs were prepared following several synthetic routes and were tested in binding assays with radioligands at 5-HT1A, D2, and α 1 receptors from rat brain membranes. Among the new derivs. trans-4-[4-(3-methoxyphenyl)cyclohexyl]-1-(2-pyridinyl)piperazine (III) and trans-N-[4-(3-methoxyphenyl)cyclohexyl]-2-(2-pyridyloxy)ethylamine (IV) emerged as active compds. These compds. can be considered as conformationally constrained analogs of I and II, resp. In fact, III and IV showed a marked enhancement in 5-HT1A receptor affinity when compared to their cis isomers. Because III was a potent and selective 5-HT1A ligand (K_i , nM: 5-HT1A = 0.028, D2 = 2194, α 1 = 767), it was chosen as a lead to prepare other analogs that were tested at 5-HT1A, D2, and α 1 receptors from rat brain membranes, showing high affinity at the 5-HT1A and selectivity vs D2 and α 1 receptors. Selected compds. were tested for their affinity at the human cloned 5-HT1A, α 1a, α 1b, α 1d receptor subtypes. They were also submitted to the [³⁵S]GTP_S binding assay stimulating the 5-HT1A receptor-mediated G-protein activation, therefore behaving as full or as partial agonists. Finally, the ability of iv administration of III to induce fore-paw treading in rats was evaluated in comparison with 8-OH-DPAT. Although the affinity (K_i) and in vitro activity (pD'2) of III at the 5-HT1A receptor were higher than those of 8-OH-DPAT, the compound was less potent than the reference standard in inducing the symptom.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 21 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:801616 HCPLUS
 DOCUMENT NUMBER: 137:27952
 TITLE: Effects of the nuclear factor- κ B inhibitors
 2-hydroxy-4-trifluoromethylbenzoic acid and aspirin on
 micturition in rats with normal and inflamed
 bladder

AUTHOR(S) : Velasco, C.; Angelico, P.; Guarneri, L.;
 Leonardi, A.; Clarke, D. E.; Testa, R.

CORPORATE SOURCE: Pharmaceutical Research and Development Division,
 Recordati S. p. A., Milan, Italy

SOURCE: Journal of Urology (Hagerstown, MD, United States)
 (2001), 166(5), 1962-1968

PUBLISHER: CODEN: JOURAA; ISSN: 0022-5347
 DOCUMENT TYPE: Lippincott Williams & Wilkins
 Journal

LANGUAGE: English

AB We examined the effects of i.v. administration of the 2 nuclear factor- κ B inhibitors aspirin and 2-hydroxy-4-trifluoromethylbenzoic acid (HTB) on bladder filling and voiding in anesthetized and conscious rats. Disappearance of isovolumic bladder contractions after i.v. administration of different doses of aspirin and HTB in anesthetized, transurethrally catheterized rats was evaluated. Cystometry was performed in conscious rats during bladder infusion with saline or diluted acetic acid as well as in those with cyclophosphamide induced cystitis. Changes in bladder capacity and voiding pressure were evaluated after i.v. administration of test compds. Aspirin induced a dose dependent disappearance of isovolumic bladder contractions in anesthetized rats with an extrapolated dose of 2.1 mg./kg. inducing 10 min of bladder quiescence. HTB was practically inactive, inducing a dose independent block of 3 to 4 min after i.v. administration of 1 to 10 mg./kg. In conscious rats with a bladder infused with saline aspirin was poorly active on bladder capacity, inducing a 20% increase 60 min after i.v. administration of 30 and 100 mg./kg. In rats with a bladder infused with acetic acid aspirin was much more active when injected at the initiation of inflammation and after 1 h of irritant infusion. In this latter situation aspirin increased bladder capacity up to 60% after i.v. administration of 30 and 100 mg./kg. Similar results were obtained in rats with cyclophosphamide induced cystitis in which the bladder was infused with saline. In these cystometrograph models 30 mg./kg. HTB i.v. was completely inactive. The results show that HTB is devoid of significant effects on the micturition reflex in the absence or presence of bladder inflammation, suggesting that acute inhibition of nuclear factor- κ B does not influence bladder urodynamics in rats. In contrast, aspirin, which is a cyclooxygenase and nuclear factor- κ B inhibitor, was always effective, indicating the important role of cyclooxygenase enzymes.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 22 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:573542 HCPLUS
 DOCUMENT NUMBER: 135:152824
 TITLE: Preparation of 1,4-disubstituted piperazines for treating neuromuscular dysfunctions of the lower urinary tract
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Guarneri, Luciano; Poggesi, Elena
 PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company, Switz.
 SOURCE: U.S., 18 pp., Cont.-in-part of U.S. Ser. No. 127,058, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

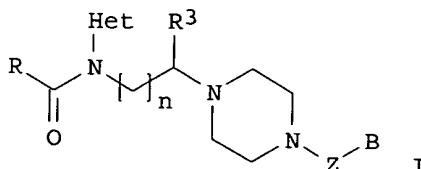
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6271234	B1	20010807	US 1999-266534	19990311
PRIORITY APPLN. INFO.:			IT 1997-MI1862	A 19970801
			IT 1997-MI1863	A 19970801
			US 1997-70266P	P 19971231
			US 1997-70267P	P 19971231

OTHER SOURCE(S) :
GI

MARPAT 135:152824

US 1998-127058

B2 19980731



AB The title compds. [I; n = 1-2; Het = monocyclic heteroaryl; R = cycloalkyl, monocyclic heteroaryl; R3 = H, alkyl; Z = bond, CH2, CH2CH2, etc.; B = (un)substituted aryl or heteroaryl], which bind to 5HT1A receptors and are therefore useful for the treatment of neuromuscular dysfunctions of the lower urinary tract, were prepared E.g., a 3-step preparation of I [R = cyclohexyl; Het = 2-pyridyl; n = 1; R3 = H; Z = bond; B = 2-(F3CO)C6H4] which showed Ki of 0.86 nM against 5-HT1A receptor binding, was given.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 23 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:335480 HCPLUS

DOCUMENT NUMBER: 135:283043

TITLE: In vitro and in vivo uroselectivity of B8805-033, an antagonist with high affinity at prostatic α 1A- vs. α 1B- and α 1D-adrenoceptors

AUTHOR(S): Eltze, Manfrid; Boer, Rainer; Michel, Martin C.; Hein, Peter; Testa, Rodolfo; Ulrich, Wolf-Rudiger; Kolassa, Norbert; Sanders, Karl H.

CORPORATE SOURCE: Research Departments, Byk Gulden, Konstanz, 78467, Germany

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2001), 363(6), 649-662

CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have investigated the pharmacol. properties of B8805-033 [(\pm)-1,3,5-trimethyl-6-[3-[4-((2,3-dihydro-2-hydroxymethyl)-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]amino]-2,4(1H,3H)-pyrimidinedione], a new α 1A-adrenoceptor (AR) selective antagonist. In radioligand binding studies, B8805-033 was 150- to 1200-fold selective for α 1A-ARs (pKi rat cerebral cortex 8.70, cloned human receptor 7.71) relative to α 1B-ARs (pKi rat cerebral cortex 5.60, rat liver 5.39, cloned human receptor 5.16) and α 1D-ARs (pKi cloned human receptor 5.49). B8805-033 inhibited noradrenaline (NA) induced contractions mediated by α 1A-ARs in rat vas deferens and rabbit and human prostate (pA2 7.62-8.40) much more potently than those mediated by α 1B-ARs in guinea pig and mouse spleen or by α 1D-ARs in rat aorta and pulmonary artery (pA2 5.21-5.52). With the exception of a high agonist affinity at 5-HT1A receptors (pKi 9.74 in pig cortex, pD2 6.82 for contraction of rabbit basilar artery) and a moderate to low affinity at histamine H1-receptors (pA2 6.74) and β 1-ARs (pA2 5.75), B8805-033 did not interact with a number of other neurotransmitter receptors (pKi or

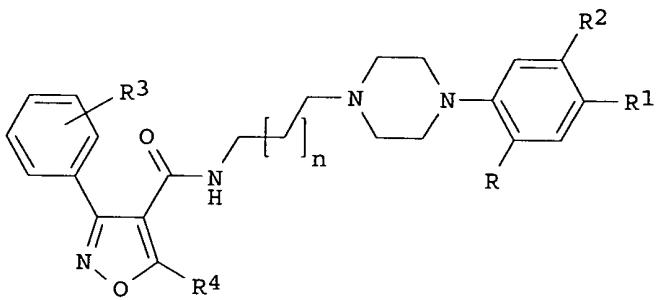
pA₂<5.0). From the i.v. doses of B8805-033 to either inhibit the urethral pressure response to NA by 50% (29 nmol/kg) or to evoke a fall in diastolic blood pressure by 25% (1.54 mmol/kg) in anesthetized dogs, an urethral/vascular selectivity ratio of 52 was obtained, far exceeding that found for the nearly unselective prazosin (ratio 1.8). We conclude that B8805-033 is a highly α 1A-AR selective antagonist, which may potentially be useful as pharmacol. tool to investigate α 1-AR heterogeneity and in the treatment of benign prostatic hyperplasia.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 24 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:300696 HCAPLUS
 DOCUMENT NUMBER: 134:311203
 TITLE: Isoxazolecarboxamide derivatives and their adrenergic antagonist activity
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo;
 Poggesi, Elena
 PATENT ASSIGNEE(S): Recordati Industria Chimica E Farmaceutica S.P.A., Italy; Recordati S.A., Chemical and Pharmaceutical Company
 SOURCE: PCT Int. Appl., 53 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029015	A2	20010426	WO 2000-EP10144	20001016
WO 2001029015	A3	20011101		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 99MI2173	A1	20010418	IT 1999-MI2173	19991018
IT 1314191	B1	20021206		
CA 2385472	AA	20010426	CA 2000-2385472	20001016
BR 2000014851	A	20020611	BR 2000-14851	20001016
EP 1226131	A2	20020731	EP 2000-992436	20001016
EP 1226131	B1	20031217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
AU 757614	B2	20030227	AU 2001-28347	20001016
JP 2003512362	T2	20030402	JP 2001-531815	20001016
NZ 517884	A	20030829	NZ 2000-517884	20001016
AT 256670	E	20040115	AT 2000-992436	20001016
PT 1226131	T	20040531	PT 2000-992436	20001016
ES 2210033	T3	20040701	ES 2000-992436	20001016
US 6365591	B1	20020402	US 2000-691778	20001018
US 2002161012	A1	20021031	US 2002-52325	20020117
US 6680319	B2	20040120		
NO 2002001803	A	20020617	NO 2002-1803	20020417

ZA 2002003942 PRIORITY APPLN. INFO.:	A 20030102	ZA 2002-3942 IT 1999-MI2173 US 2000-218314P WO 2000-EP10144 US 2000-691778	20020517 A 19991018 P 20000714 W 20001016 A3 20001018
OTHER SOURCE(S) : GI	MARPAT 134:311203		



AB Isoxazolecarboxamides I (R = alkyl, alkoxy, polyfluoroalkoxy, OH, CF₃SO₂O; R₁, R₂ = H, halo, polyfluoroalkoxy, alkoxy; R₃ = one or more substituents selected from H, halo, alkyl, alkoxy, NO₂, NH₂, NHacyl, CN, alkoxy carbonyl, carboxamido; R₄ = H, alkyl, aralkyl; n = 0, 1, 2) and their N-oxides and pharmaceutically acceptable salts are prepared for their adrenergic antagonist activity and high selectivity toward the α 1a adrenergic receptor with respect to the 5-HT1A receptor. This activity profile suggests the use of these derivs. in the treatment of obstructive syndromes of the lower urinary tract, including BPH, without side effects associated with hypotensive activity. Thus, I (R = MeO, R₁ = R₃ = H, R₂ = Cl, R₄ = Me) was prepared in 3 steps from 1-(5-chloro-2-methoxyphenyl)piperazine and N-(3-bromopropyl)phthalimide via 1-(5-chloro-2-methoxyphenyl)-4-(3-phthalimidopropyl)piperazine and 1-(3-aminopropyl)-4-(5-chloro-2-methoxyphenyl)piperazine trihydrochloride.

L69 ANSWER 25 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:141864 HCAPLUS
 DOCUMENT NUMBER: 135:147110
 TITLE: Effect of different 5-hydroxytryptamine receptor subtype antagonists on the micturition reflex in rats
 AUTHOR(S): Testa, R.; Guarneri, L.; Angelico, P.; Velasco, C.; Poggesi, E.; Cilia, A.; Leonardi, A.
 CORPORATE SOURCE: Pharmaceutical R & D Division, Recordati S.p.A., Milan, Italy
 SOURCE: BJU International (2001), 87(3), 256-264
 CODEN: BJINFO; ISSN: 1464-4096
 PUBLISHER: Blackwell Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Objective To evaluate the effects of antagonists of different subfamilies of 5-hydroxytryptamine (5-HT) receptors on bladder function in anesthetized and conscious rats. Materials and methods The urinary bladder of female anesthetized rats was

catheterized urethrally and filled with physiol. saline until spontaneous bladder contractions occurred. Infravesical pressure was measured by a pressure transducer and displayed continuously on a chart recorder. The time of bladder quiescence (to the disappearance of rhythmic contractions) after injection with different compds. tested was recorded. Conscious rats underwent cytometry with chronically (infravesical) implanted catheters to continuously record bladder capacity (evaluated as amount of saline infused between voiding cycles) and maximal voiding pressure. The affinity for the human recombinant serotoninergic 5-HT_{1A} subtype (inhibition of specific binding of [³H]8-hydroxy-2-(di-n-propylamino) tetralin) and the effects on the [³⁵S]guanosine 5'-(γ -thio) triphosphate (GTP γ S) binding in HeLa cells was also evaluated. Results Among the compds. tested, only 4-(2'-methoxy-phenyl)-1-[2'-(n-2"-pyridinyl)-p-iodobenzamido]-ethyl-piperazine (p-MPPI) and methiothepin showed nanomolar affinity for the 5-HT_{1A} receptors, the former being a neutral antagonist and the latter an inverse agonist in the [³⁵S]GTP γ S binding model. I.v. injection of low doses of p-MPPI and methiothepin induced a dose-dependent disappearance of isovolumic bladder contractions in anesthetized rats (>10 min). At the highest doses, the dose-response curves were bell-shaped. The amplitude of bladder contractions was not markedly altered. The tested antagonists of 5-HT₂, 5-HT₃, 5-HT₄, and 5-HT₆ serotoninergic subtypes were poorly active or inactive in the model. Similarly, these compds. were inactive on cytometry in conscious rats, whereas p-MPPI and methiothepin induced a consistent increase in bladder capacity. Methiothepin also decreased the voiding pressure, whereas p-MPPI did not affect this variable. Conclusions These findings confirm that only selective 5-HT_{1A} receptor antagonists have favorable effects on the bladder, inducing an increase in bladder capacity with no derangement of bladder contractility.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

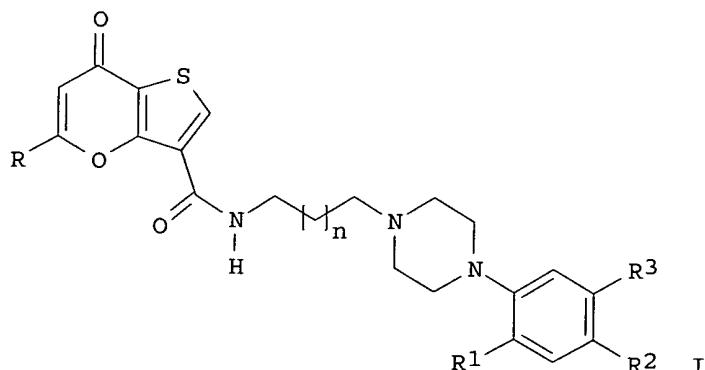
L69 ANSWER 26 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:101147 HCAPLUS
 DOCUMENT NUMBER: 134:163064
 TITLE: Preparation of thienopyranecarboxamides with enhanced selectivity for the α 1 adrenergic receptor
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati Industria Chimica E Farmaceutica Spa, Italy; Recordati S.A., Chemical and Pharmaceutical Company
 SOURCE: PCT Int. Appl., 42 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009140	A1	20010208	WO 2000-EP7306	20000728
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

IT 99MI1704	A1	20010130	IT 1999-MI1704	19990730
CA 2378302	AA	20010208	CA 2000-2378302	20000728
US 6306861	B1	20011023	US 2000-627766	20000728
BR 2000012871	A	20020416	BR 2000-12871	20000728
EP 1200445	A1	20020502	EP 2000-958313	20000728
EP 1200445	B1	20030917		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6387909	B1	20020514	US 2000-627767	20000728
JP 2003506379	T2	20030218	JP 2001-514343	20000728
AU 759085	B2	20030403	AU 2000-69882	20000728
AT 250068	E	20031015	AT 2000-958313	20000728
PT 1200445	T	20040227	PT 2000-958313	20000728
RU 2225409	C2	20040310	RU 2002-105022	20000728
ES 2206296	T3	20040516	ES 2000-958313	20000728
US 6486163	B2	20021126	US 2001-931153	20010816
US 2002193381	A1	20021219		
ZA 2002000687	A	20020731	ZA 2002-687	20020125
NO 2002000476	A	20020129	NO 2002-476	20020129
HK 1044763	A1	20040423	HK 2002-105973	20020815
PRIORITY APPLN. INFO.:				
		IT 1999-MI1704	A	19990730
		US 2000-179423P	P	20000131
		US 2000-627766	A3	20000728
		WO 2000-EP7306	W	20000728

OTHER SOURCE(S) : MARPAT 134:163064
 GI



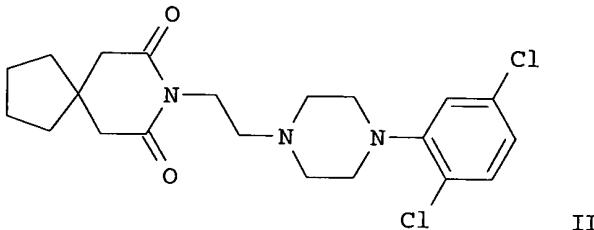
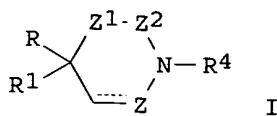
AB The title compds. [I; R = aryl, cycloalkyl, polyhaloalkyl; R1 = alkyl, alkoxy, polyfluoroalkoxy, etc.; R2, R3 = H, halo, alkoxy, polyfluoroalkoxy; n = 0-2] and their pharmaceutically acceptable salts which are endowed with enhanced selectivity for the α_1 adrenergic receptor and a low activity in lowering blood pressure, and are useful in the treatment of obstructive syndromes of the lower urinary tract, including benign prostatic hyperplasia (BPH), in lowering intraocular pressure, in the treatment of cardiac arrhythmia and erectile and sexual dysfunction, and in the treatment of lower urinary tract symptoms (LUTS) and neurogenic lower urinary tract dysfunction (NLUTD), were prepared E.g., a multi-step synthesis of I [R = Ph; R1 = OMe; R2 = H; R3 = Cl; n = 1] which showed pK_b of 8.17 against

α 1L adrenoceptor subtype binding, was given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 27 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:63974 HCAPLUS
 DOCUMENT NUMBER: 134:115867
 TITLE: Preparation of azaspirodecane(diones and analogs as
 α 1D adrenoceptor antagonists
 INVENTOR(S): Leonardi, Amedeo; Barlocco, Daniela; Motta, Gianni;
 Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati Industria Chimica e Farmaceutica S.p.A.,
 Italy; Recordati S.A., Chemical and Pharmaceutical
 Company
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIIXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005765	A1	20010125	WO 2000-EP6738	20000714
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 99MI1578	A1	20010115	IT 1999-MI1578	19990715
EP 1200406	A1	20020502	EP 2000-945917	20000714
EP 1200406	B1	20041124		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505375	T2	20030212	JP 2001-511426	20000714
AT 283261	E	20041215	AT 2000-945917	20000714
PRIORITY APPLN. INFO.:			IT 1999-MI1578	A 19990715
			WO 2000-EP6738	W 20000714
OTHER SOURCE(S):	MARPAT	134:115867		
GI				



AB Title compds. [I; R, R1 = H or alkyl; RR1 = (CH₂)₂₋₆; R⁴ = CHR₃CHR₇CHR₃; R₃ = H or alkyl; R⁷ = Z₃Z₄R₂; R₂ = halo, alkyl, cyano; Z = CH₂, CO, CH; Z₁ = bond or CH₂; Z₂ = CH₂ or CO; Z₃ = piperidine- or -azine-1,4-diyl or NMe(CH₂)_mZ₅Z₄R₂; Z₄ = (un)substituted 1,2-phenylene; Z₅ = O, S, NH, NMe; m = 2-4; dashed line = optional addnl. bond] were prepared. Thus, 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione was aminated by 1-(2,5-dichlorophenyl)piperazine to give title compound II. Data for biol. activity of I were given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 28 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2000:814291 HCPLUS
 DOCUMENT NUMBER: 133:359253
 TITLE: Use of selective antagonists of the α lb-adrenergic receptor for improvement of sexual dysfunction
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Testa, Rodolfo; Sironi, Giorgio
 PATENT ASSIGNEE(S): Recordati Industria Chimica E Farmaceutica S.p.A., Italy; Recordati S.A., Chemical and Pharmaceutical Co.
 SOURCE: PCT Int. Appl., 46 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

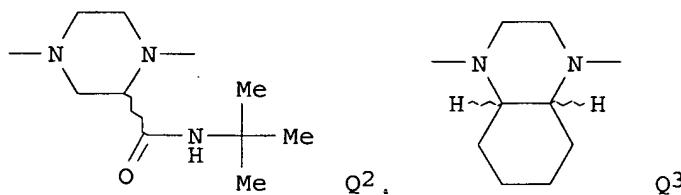
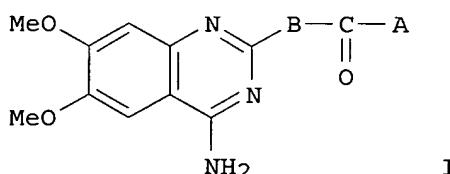
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067735	A2	20001116	WO 2000-EP4308	20000508
WO 2000067735	A3	20010201		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

IT 99MI0995	A1	20001107	IT 1999-MI995	19990507
IT 1312310	B1	20020415		
TW 224503	B1	20041201	TW 2000-89108045	20000427
US 6303606	B1	20011016	US 2000-565842	20000505
CA 2366201	AA	20001116	CA 2000-2366201	20000508
EP 1177190	A2	20020206	EP 2000-927199	20000508
EP 1177190	B1	20051102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010348	A	20020213	BR 2000-10348	20000508
JP 2002544158	T2	20021224	JP 2000-616762	20000508
AU 765487	B2	20030918	AU 2000-45654	20000508
NZ 515240	A	20030926	NZ 2000-515240	20000508
RU 2239633	C2	20041110	RU 2001-133004	20000508
AT 308538	E	20051115	AT 2000-927199	20000508
ES 2250130	T3	20060416	ES 2000-927199	20000508
US 2002161009	A1	20021031	US 2001-935288	20010822
US 6953800	B2	20051011		
NO 2001005428	A	20011106	NO 2001-5428	20011106
ZA 2001010042	A	20020702	ZA 2001-10042	20011206
HK 1039900	A1	20060203	HK 2002-101448	20020226
PRIORITY APPLN. INFO.:				
			IT 1999-MI995	A 19990507
			US 2000-183257P	P 20000217
			US 2000-565842	A1 20000505
			WO 2000-EP4308	W 20000508

OTHER SOURCE(S) :

MARPAT 133:359253

GI



AB Compds. I (A = 2-furyl, substituted 2-furyl, 2-tetrahydrofuryl, substituted alkoxy, substituted phenoxyalkyl; B = 1,4-piperazinediyl, Q², Q³; if B = 1,4-piperazinediyl then A = substituted phenoxyalkyl) and their enantiomers, diastereoisomers, and pharmaceutically acceptable salts are useful for the preparation of a medicament for the treatment of sexual dysfunction in males and females. Compds. II (I, B=Q³, A ≠ 2-furyl) are novel and are claimed per se. Pharmaceutical compns. containing II are also claimed, as are pharmaceutical compns. containing compds. I and one or more of a prostaglandin, a direct vasodilator and a type 5 cGMP phosphodiesterase inhibitor (e.g. sildenafil). Compds. which bind to mammalian α_{1B} adrenergic receptors with an affinity of at least about 10⁻⁸ M and which bind to mammalian α_{1B} adrenergic receptors with an affinity at least 10-fold higher than the affinity with which the

compound binds to mammalian α 1a or α 1d or α 1L adrenergic receptors are also useful for the preparation of a medicament for the treatment of sexual dysfunction in males and females. A method of identifying such compds. is also disclosed and claimed.

L69 ANSWER 29 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:237739 HCPLUS
DOCUMENT NUMBER: 133:12230
TITLE: α 1-Adrenoceptor antagonists bearing a quinazoline or a benzodioxane moiety
AUTHOR(S): Melchiorre, C.; Angeli, P.; Bolognesi, M. L.; Chiarini, A.; Giardina, D.; Gulini, U.; Leonardi, A.; Marucci, G.; Minarini, A.; Pigini, M.; Quaglia, W.; Rosini, M.; Tumiatti, V.
CORPORATE SOURCE: Via Belmeloro 6, Department of Pharmaceutical Sciences, University of Bologna, Bologna, 40126, Italy
SOURCE: Pharmaceutica Acta Helveticae (2000), 74(2-3), 181-190
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. on design, structure-activity relationships, and pharmacol. of the title compds.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 30 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:171777 HCPLUS
DOCUMENT NUMBER: 132:303466
TITLE: Effects of intracavernous administration of selective antagonists of α 1-adrenoceptor subtypes on erection in anesthetized rats and dogs
AUTHOR(S): Sironi, Giorgio; Colombo, Davide; Poggesi, Elena; Leonardi, Amedeo; Testa, Rodolfo; Rampin, Olivier; Bernabe, Jacques; Giuliano, Francois
CORPORATE SOURCE: Pharmaceutical R and D Division, Milan, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(3), 974-981
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The proerectile properties of three novel α 1-adrenoceptor (α 1-ADR) antagonists with different profiles of selectivity for the α 1-ADR subtypes have been evaluated in anesthetized rats and dogs on intracavernous (IC) injection, in comparison with prazosin and phentolamine. In rats, the tested compds. decreased blood pressure (BP) and increased IC pressure (ICP), as well as the ratio ICP/BP. Rec 15/2841 (α 1a- plus α 1L-ADR-selective antagonist) and Rec 15/2615 (α 1b-ADR selective) were the most potent compds. The ICP/BP ratios calculated after injection of Rec 15/3039 (α 1d-ADR selective) were not markedly different from those observed after vehicle injection. Prazosin and phentolamine proved poorly active, their main effect being hypotension. Approx. ED25 values (dose of compound in micrograms inducing 25% increase of ICP/BP ratio) were Rec 15/2615 (22 μ g/kg) \geq Rec 15/2841 (29 μ g/kg) $>$ prazosin (136 μ g/kg) $>$ phentolamine (1298 μ g/kg) $>$ Rec 15/3039 (9600 μ g/kg). Submaximal stimulation of the cavernous nerve elicited an ICP rise whose amplitude

was not altered by Rec compds. In contrast, prazosin and phentolamine decreased this ICP rise. All compds. but 15/3039 induced significant increase of the ICP/BP ratio in dogs. Rec 15/2615 proved to be the most interesting compound, inducing significant increases of ICP/BP at doses practically devoid of effects on BP. The rank order of potency in dog in increasing the ICP/BP ratio was similar to that observed in rats. Only at the highest doses tested, all compds., except Rec 15/3039, decreased the ICP rise elicited by submaximal stimulation of the cavernous nerve. Our data demonstrate that the α 1b- and α 1L-ADR subtypes are functionally relevant for the erectile function in these models, and that α 1b- and/or α 1L-ADR subtypes selective antagonists could represent a real advantage in erectile dysfunction therapy.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 31 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:547948 HCPLUS

DOCUMENT NUMBER: 131:281021

TITLE: Effect of several 5-hydroxytryptamine1A receptor ligands on the micturition reflex in rats: comparison with WAY 100635

AUTHOR(S): Testa, R.; Guarneri, L.; Poggesi, E.; Angelico, P.; Velasco, C.; Ibba, M.; Cilia, A.; Motta, G.; Riva, C.; Leonardi, A.

CORPORATE SOURCE: Pharmaceutical Research and Development Division, Milan, Italy

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 290(3), 1258-1269

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several novel N-arylpiperazine derivs. were synthesized and tested for their (1) affinity and functional activity on 5-hydroxytryptamine1A (5-HT1A) receptors in vitro; (2) activity in models predictive of antagonism at somatodendritic and postsynaptic 5-HT1A receptors; (3) and effects on the micturition reflex in anesthetized and conscious rats. These studies also included 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine hydrobromide (NAN 190), 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7, 9-dione dihydrochloride (BMY 7378), and N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide (WAY 100635). Almost all compds. were found to be potent and selective for the human recombinant 5-HT1A receptor, with Ki values in the nanomolar range. [35S]GTP γ S binding in HeLa cells expressing the recombinant human 5-HT1A receptor allowed classification of the compds. into neutral antagonists and partial agonists. Almost all neutral antagonists were active in blocking 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT)-induced forepaw treading in rats (postsynaptic model) and hypothermia in mice (somatodendritic model) with the same potency, whereas compds. showing partial agonistic activity were active in the postsynaptic model but were inactive, or poorly active, in the somatodendritic model. Neutral antagonists potently inhibited volume-induced bladder-voiding contractions in anesthetized rats. Contractions were completely blocked, and the disappearance of bladder contractions lasted 7 to 13 min after the highest doses tested. Furthermore, neutral antagonists increased bladder volume capacity in conscious rats during continuous transvesical cystometry, whereas micturition pressure was only slightly, and not dose-dependently,

reduced. Partial agonists were inactive or poorly active, inducing a disappearance time of bladder contractions that did not exceed 6 min in anesthetized rats, and failing to increase bladder volume capacity in conscious rats. These findings indicate that only neutral 5-HT_{1A} receptor antagonists are endowed with inhibitory effects on the bladder.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 32 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:514813 HCPLUS
 DOCUMENT NUMBER: 131:266572
 TITLE: Vascular-selective effect of lercanidipine and other 1,4-dihydropyridines in isolated rabbit tissues
 AUTHOR(S): Angelico, P.; Guarneri, L.; Leonardi, A.; Testa, R.
 CORPORATE SOURCE: Pharmaceutical R & D Division, Recordati S.p.A., Milan, 1-20148, Italy
 SOURCE: Journal of Pharmacy and Pharmacology (1999), 51(6), 709-714
 CODEN: JPPMAB; ISSN: 0022-3573
 PUBLISHER: Royal Pharmaceutical Society of Great Britain
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The aim of this study was to characterize the in-vitro vasoselectivity of lercanidipine (in comparison with lacidipine, amlodipine, nitrendipine and felodipine) by evaluating its functional calcium antagonistic activity on rabbit vascular (aorta) and cardiac tissues (heart ventricle). Although incubation with all the compds. tested elicited a concentration-dependent relaxant effect on vascular tissue precontracted with KCl (80 mM), 50% relaxation was reached at different times for each concentration and drug tested.

At 10 nM concentration 50% relaxation was reached after 210 min with lercanidipine, 278 min with amlodipine, 135 min with lacidipine, 75 min with nitrendipine and 70 min with felodipine. The onset of the effect was, therefore, similar for lercanidipine, amlodipine and lacidipine, but faster for nitrendipine and felodipine. Similarly, all the compds. tested concentration-dependently reduced the force of cardiac contraction (neg. inotropic activity). In this model, the time needed to reach 50% reduction in contractile force was also concentration-dependent, and the ranking order of

the speed of onset of the effect (evaluated as the ratio of the IC₅₀ values (the concns. inhibiting contraction by 50%) calculated after 1 and 4 h incubation) was lacidipine (3.8) > amlodipine (9.6) > felodipine (39) > lercanidipine (68) = nitrendipine (89). The vasoselectivity, expressed as the ratio of the IC₅₀ values obtained on cardiac and vascular tissue, were (for 4 h incubation) 730, 193, 95, 6 and 3 for lercanidipine, lacidipine, amlodipine, felodipine and nitrendipine, resp., showing that lercanidipine is the most vasoselective of the calcium-antagonists tested. The results show that lercanidipine reduces the inotropic force of the rabbit heart to a lesser extent than do other calcium antagonists, and that this drug had the best heart/vessel selectivity index among the compds. tested at all the times tested.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 33 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:394166 HCPLUS
 DOCUMENT NUMBER: 131:193730
 TITLE: Effects of α -adrenoceptor antagonists on



agonist and tilt-induced changes in blood pressure:
relationships to uroselectivity

AUTHOR(S) : Hieble, J. Paul; Kolpak, David C.; McCafferty, Gerald P.; Ruffolo, Robert R., Jr.; Testa, Rodolfo; Leonardi, Amedeo

CORPORATE SOURCE: UW2510, Division of Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA

SOURCE: European Journal of Pharmacology (1999), 373(1), 51-62
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We evaluated the uroselectivity of a series of α_1 -adrenoceptor antagonists by comparing their potency against phenylephrine-induced increases in urethral perfusion pressure and diastolic blood pressure in the anesthetized rabbit and pithed rat. In the rabbit, Rec 15/2739 (N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide) as well as analogs with a chlorine substituent on the methoxyphenyl ring (Rec 15/2869) or this substituent combined with the replacement of the Ph substituent on the pyran ring by cyclohexyl (Rec 15/3011) were 2-6-fold more potent against the urethral vs. vascular response to phenylephrine. Rec 15/2841 (N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-cyclohexyl-4H-1-benzopyran-8-carboxamide) was only 1.5-fold more potent against the urethral response. SL 89.0591 and tamsulosin also showed selectivity for the urethral response (2-2.5-fold), while the quinazolines produced equipotent blockade of urethral and vascular responses (selectivity ratio=0.9-1.1). The urethral selectivities of Rec 15/2739 and its derivs. were confirmed by evaluation of the response to tilt in sedated, hypovolemic rabbits. Phenylephrine challenge assays did not show any of the antagonists, with the exception of terazosin at 300 μ g kg⁻¹, to be uroselective in the rat (selectivity ratios=0.2-1.5); potentiation of tilt-induced hypotension in the anesthetized rat showed substantial differences from the rabbit, with Rec 15/2739, but not Rec 15/3011 and Rec 15/2841 showing orthostatic effects equivalent to that observed for prazosin. Hence, Rec 15/2739 was uroselective in the rabbit, but not in the rat, while two of its close structural analogs were highly uroselective in both species. An assay for orthostatic activity in the conscious rat yielded different results, showing prazosin and terazosin, but not Rec 15/2739, to cause a reversal of the pressor response to tilt. Hence, the apparent uroselectivity of an α_1 -adrenoceptor antagonist is both species- and assay-dependent.

IT 19216-56-9 63590-64-7 74191-85-8,

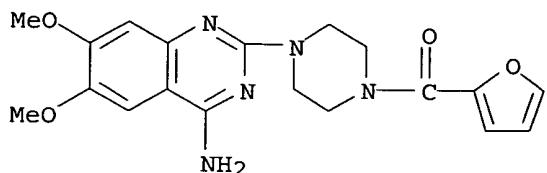
Doxazosin 81403-80-7, Alfuzosin

106133-20-4, Tamsulosin

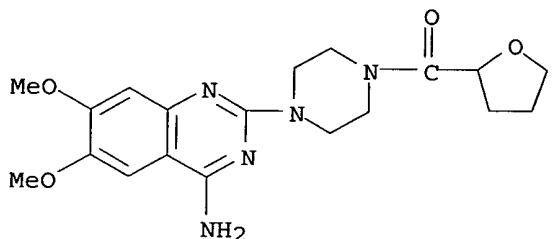
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of α_1 -adrenoceptor antagonists on agonist and tilt-induced changes in blood pressure and structure-activity relationships to uroselectivity)

RN 19216-56-9 HCAPLUS

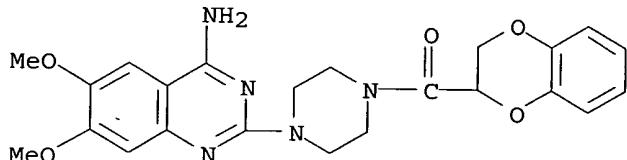
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



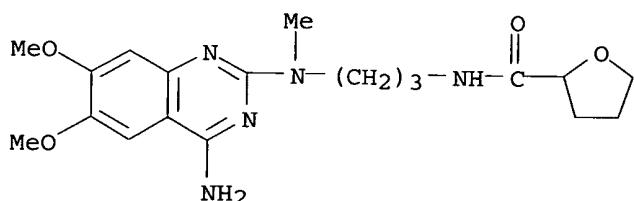
RN 63590-64-7 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]- (9CI) (CA INDEX NAME)



RN 74191-85-8 HCAPLUS
 CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]- (9CI) (CA INDEX NAME)

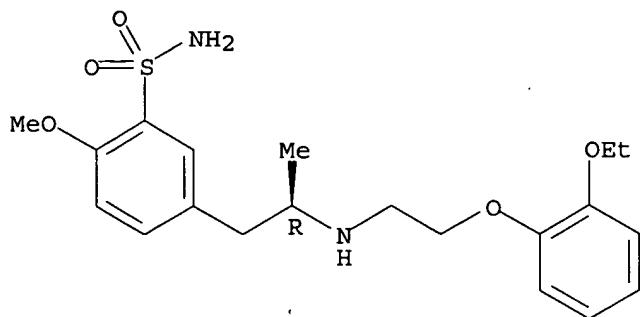


RN 81403-80-7 HCAPLUS
 CN 2-Furancarboxamide, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro- (9CI) (CA INDEX NAME)



RN 106133-20-4 HCAPLUS
 CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 34 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:113661 HCPLUS
 DOCUMENT NUMBER: 130:168397
 TITLE: Preparation of 1-[(phenylamino)alkyl]piperazines as 5-HT1A receptor antagonists
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company, Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906384	A1	19990211	WO 1998-EP4804	19980731
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2297095	AA	19990211	CA 1998-2297095	19980731
AU 9891578	A1	19990222	AU 1998-91578	19980731
AU 737456	B2	20010823		
EP 1000047	A1	20000517	EP 1998-943815	19980731
EP 1000047	B1	20031217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NZ 502804	A	20010223	NZ 1998-502804	19980731
JP 2001512112	T2	20010821	JP 2000-505143	19980731
BR 9811482	A	20020122	BR 1998-11482	19980731
RU 2199533	C2	20030227	RU 2000-105266	19980731
CN 1127493	B	20031112	CN 1998-807820	19980731
AT 256671	E	20040115	AT 1998-943815	19980731
MX 200000943	A	20001026	MX 2000-943	20000127
NO 2000000521	A	20000201	NO 2000-521	20000201

NO 315232 B1 20030804
 PRIORITY APPLN. INFO.: IT 1997-MI1864 A 19970801
 WO 1998-EP4804 W 19980731
 OTHER SOURCE(S) : MARPAT 130:168397
 AB 2-R2C6H4NRCH2CHR1ZR3 (Z = piperazine-1,4-diyl) [I; R = H, alkanoyl, heteroarylcarbonyl, etc.; R1 = H or alkyl; R2 = halo, (acyl)amino, alkoxy carbonyl, etc.; R3 = (hetero)aryl, substituted CH₂Ph, etc.] were prepared. Thus, 2-ClC₆H₄NO₂ was aminated by 1-(2-aminoethyl)-2-(2-methoxyphenyl)piperazine to give I [R = R1 = H, R2 = NO₂, R3 = C₆H₄(OMe)-2]. Data for biol. activity of I were given.
 REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 35 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:113660 HCPLUS
 DOCUMENT NUMBER: 130:168396
 TITLE: Preparation of 1-(3,3-diarylpropyl)piperazines and analogs for treatment of urinary dysfunction
 INVENTOR(S) : Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S) : Recordati S.A., Chemical and Pharmaceutical Company, Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.
 SOURCE: PCT Int. Appl., 37 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906383	A1	19990211	WO 1998-EP4797	19980731
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9891576	A1	19990222	AU 1998-91576	19980731
EP 1000046	A1	20000517	EP 1998-943811	19980731
EP 1000046	B1	20031126		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001512111	T2	20010821	JP 2000-505142	19980731
AT 255094	E	20031215	AT 1998-943811	19980731
PT 1000046	T	20040430	PT 1998-943811	19980731
ES 2212339	T3	20040716	ES 1998-943811	19980731
US 6894052	B1	20050517	US 1998-127059	19980731
PRIORITY APPLN. INFO. :			IT 1997-MI1861	A 19970801
			US 1997-70269P	P 19971231
			WO 1998-EP4797	W 19980731

OTHER SOURCE(S) : MARPAT 130:168396
 AB R3CH2CHRZR4 (Z = piperazine-1,4-diyl) [I; R = H or alkyl; R3 = R₁R₂N, R₁R₂CH, R₁R₂C(N), etc.; R₁,R₂ = (un)substituted (hetero)aryl; R₄ = (hetero)aryl], 5-HT_{1A} receptor ligands, were prepared. Thus, 1-(2-methoxyphenyl)piperazine was amidated by Ph₂CHCH₂CO₂H and the product reduced to give Ph₂CHCH₂CH₂ZC₆H₄(OMe)-2. Data for biol. activity of I

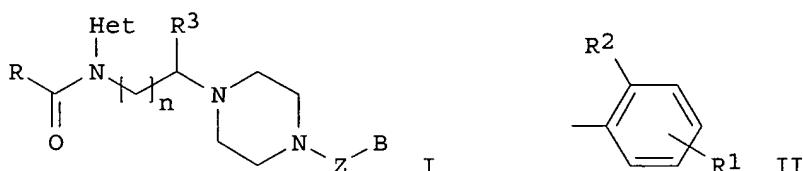
were given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 36 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:113659 HCAPLUS
 DOCUMENT NUMBER: 130:182480
 TITLE: Preparation of 1,4-disubstituted piperazines for treating neuromuscular dysfunctions of the lower urinary tract
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Guarneri, Luciano; Poggesi, Elena
 PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company, Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.
 SOURCE: PCT Int. Appl., 37 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906382	A1	19990211	WO 1998-EP4796	19980731
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9892564	A1	19990222	AU 1998-92564	19980731
EP 1000045	A1	20000517	EP 1998-945130	19980731
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001512110	T2	20010821	JP 2000-505141	19980731
PRIORITY APPLN. INFO.:			IT 1997-MI1862	A 19970801
			IT 1997-MI1863	A 19970801
			WO 1998-EP4796	W 19980731

OTHER SOURCE(S): MARPAT 130:182480
 GI



AB The title compds. [I; n = 1-2; Het = monocyclic heteroaryl; R = cycloalkyl, monocyclic heteroaryl; R3 = H, lower alkyl; Z = bond, CH2, CH2CH2, etc.; B = (un)substituted aryl or heteroaryl], which bind to 5HT1A receptors and are therefore useful for the treatment of neuromuscular dysfunctions of the lower urinary tract, were prepared E.g., a 3-step preparation of I [R = cyclohexyl; Het = 2-pyridyl;

$n = 1$; $R3 = H$; $Z = \text{bond}$; $B = 2-(F_3CO)C_6H_4$] which showed K_i of 0.86 nM against 5-HT_{1A} receptor binding. The compds. I in which $Z = \text{bond}$; $B = II$ [$R1 = H$, halo, alkoxy, etc.; $R2 = \text{halo, alkoxy, polyfluoroalkoxy, etc.}$; provided that if $R1 = NH(\text{acyl})$ or $NHSO_2(\text{alkyl})$ then $R2 = \text{polyfluoroalkoxy}$] and the compds. I in which $Z = CH_2, CH_2CH_2, CH_2C(O), CH_2CH(OH), O, OCH_2$ or $C(O)$ are claimed per se; other compds. are claimed for use in preparation of medicaments for treating neuromuscular dysfunctions of the lower urinary tract.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 37 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:89741 HCPLUS

DOCUMENT NUMBER: 130:276225

TITLE: Synthesis, Pharmacological Evaluation, and Structure-Activity Relationship and Quantitative Structure-Activity Relationship Studies on Novel Derivatives of 2,4-Diamino-6,7-dimethoxyquinazoline α_1 -Adrenoceptor Antagonists

AUTHOR(S): Leonardi, Amedeo; Motta, Gianni; Boi, Carlo; Testa, Rodolfo; Poggesi, Elena; De

CORPORATE SOURCE: Benedetti, Pier G.; Menziani, M. Cristina

SOURCE: Recordati S.p.A., Milan, 20148, Italy
Journal of Medicinal Chemistry (1999), 42(3), 427-437

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new series of novel piperazine and non-piperazine derivs. of 2,4-diamino-6,7-dimethoxyquinazoline was synthesized and evaluated for binding affinity toward α_1 -adrenergic and other G-protein-coupled aminergic receptors. The α_1 -adrenoceptor (AR) subtype selectivity was also investigated for the most interesting compds. Only 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2-isopropyl-6-methoxyphenoxy)acetyl]piperazene showed moderate selectivity toward the α_{1B} -AR subtype. Selected compds. were tested in vivo in a dog model indicating activity on blood pressure and on the lower urinary tract. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(benzoylacetyl)piperazine showed in vivo potency close to that of prazosin. Powerful interpretative and predictive theor. QSAR models have been obtained. The theor. descriptors employed in the rationalization of the α_1 -adrenergic binding affinity depict the key features for receptor binding which can be summarized in an electrostatic interaction between the protonated amine function and a primary nucleophilic site of the receptor, complemented by short-range attractive (polar and dispersive) and repulsive (steric) intermol. interactions. Moreover, on predictive grounds, the ad hoc derived size and shape QSAR model developed in a previous paper (Rastelli, G.; et al. J. Mol. Struct. 1991, 251, 307-318) proved to be successful in predicting nanomolar α_1 -adrenergic binding affinity for 4-amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydrobenz[f]isoquinolin-2-yl)quinazoline.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 38 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:686073 HCPLUS

DOCUMENT NUMBER: 130:66462

TITLE: Design, synthesis, and biological activity of prazosin-related antagonists. Role of the piperazine and furan units of prazosin on

AUTHOR(S) :

the selectivity for $\alpha 1$ -adrenoreceptor subtypes
 Bolognesi, Maria L.; Budriesi, Roberta; Chiarini,
 Alberto; Poggesi, Elena; Leonardi, Amedeo;
 Melchiorre, Carlo

CORPORATE SOURCE:

Department of Pharmaceutical Sciences, University of
 Bologna, Bologna, 40126, Italy

SOURCE:

Journal of Medicinal Chemistry (1998), 41(24),
 4844-4853

PUBLISHER:

CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE:

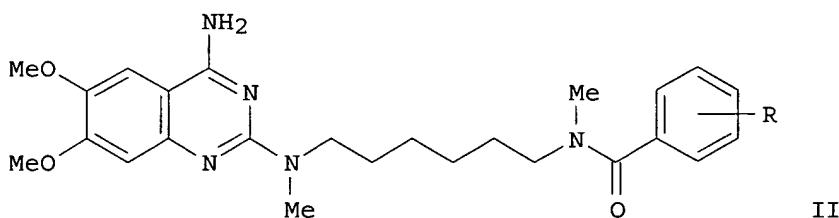
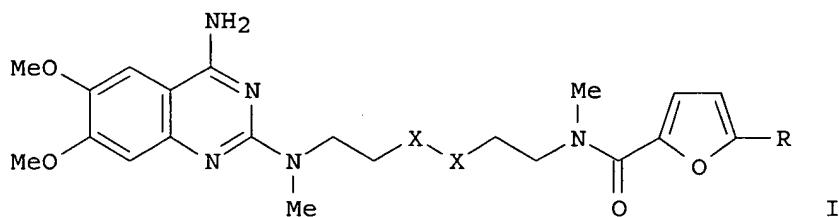
American Chemical Society

LANGUAGE:

Journal

GI

English



- AB Prazosin-related quinazolines I ($X = S$, CH_2 ; $R = CH_2Cl$, CH_2NMe_2) and II ($R = H$, $2-CH_2Cl$, 3 -thiazolidinylmethyl, etc.) were prepared and their biol. profiles at $\alpha 1$ -adrenoreceptor subtypes were assessed by functional expts. in isolated rat vas deferens ($\alpha 1A$), spleen ($\alpha 1B$), and aorta ($\alpha 1D$) and by binding assays in CHO cells expressing human cloned $\alpha 1$ -adrenoreceptor subtypes. The replacement of piperazine and furan units of prazosin by 1,6-hexanediamine and Ph moieties markedly affected both affinity and selectivity for $\alpha 1$ -adrenoreceptor subtypes in functional expts. Cystazosin I ($R = H$, $X = S$) (III), bearing a cystamine moiety, was a selective $\alpha 1D$ -adrenoreceptor antagonist being 1 order of magnitude more potent at $\alpha 1D$ -adrenoreceptors than at the $\alpha 1A$ - and $\alpha 1B$ -subtypes. The insertion of substituents on the furan ring of III did not improve the selectivity profile. The simultaneous replacement of both piperazine and furan rings of prazosin gave II ($R = H$) (IV) which resulted in a potent, selective $\alpha 1B$ -adrenoreceptor antagonist (85- and 15-fold more potent than at $\alpha 1A$ - and $\alpha 1D$ -subtypes, resp.). The insertion of substituents on the benzene ring of IV affected, according to the type and the position of the substituent, affinity and selectivity for $\alpha 1$ -adrenoreceptors. Consequently, the insertion of appropriate substituents in the Ph ring of IV may represent the basis of designing new selective ligands for $\alpha 1$ -adrenoreceptor subtypes. Interestingly, the finding that

polyamines II [R = 2-CH₂NMe(CH₂)₆NHMe, 3-CH₂NMe(CH₂)₆NHMe, 4-CH₂NMe(CH₂)₆NHMMe], bearing a 1,6-hexanediamine moiety, retained high affinity for α 1-adrenoreceptor subtypes suggests that the substituent did not give rise to neg. interactions with the receptor. Finally, binding assays performed with selected quinazolines produced affinity results, which were not in agreement with the selectivity profiles obtained from functional expts. This rather surprising and unexpected finding may be explained by considering neutral and neg. antagonism.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 39 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1998:58603 HCPLUS
 DOCUMENT NUMBER: 128:175676
 TITLE: Lercanidipine (Rec 15/2375): a novel 1,4-dihydropyridine calcium antagonist for hypertension
 AUTHOR(S): Testa, R.; Leonardi, A.; Tajana, A.; Riscassi, E.; Magliocca, R.; Sartani, A.
 CORPORATE SOURCE: Pharmaceutical RandD Division, Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Cardiovascular Drug Reviews (1997), 15(3), 187-219
 PUBLISHER: Neva Press
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 76 refs.
 REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 40 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1997:713805 HCPLUS
 DOCUMENT NUMBER: 128:18928
 TITLE: Antagonism to noradrenaline-induced lethality in rats is related to affinity for the α 1A-adrenoceptor subtype
 AUTHOR(S): Testa, Rodolfo; Guarneri, Luciano; Ibba, Marina; Angelico, Patrizia; Poggesi, Elena; Taddei, Carlo; Motta, Gianni; Leonardi, Amedeo
 CORPORATE SOURCE: Pharmaceutical RandD Division, RECORDATI S.p.A., Milan, 20148, Italy
 SOURCE: Life Sciences (1997), 61(22), 2177-2188
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The potency of several α 1-adrenoceptor antagonists in preventing the noradrenaline-induced lethality in conscious rats, their binding affinity for the native α 1A- and α 1B-adrenoceptors, the recombinant animal α 1a-, α 1b- and α 1d-adrenoceptor subtypes, as well as their functional affinity for the α 1L-adrenoceptor subtype were evaluated. The potency of the tested compds. as antagonists of noradrenaline-induced lethality was correlated with the affinity for the α 1A- (and α 1a-) adrenoceptor subtype, but not with the affinity for the other subtypes. On the contrary, the hypotensive effects of the compds., assessed in anesthetized rats, were not clearly related with the affinity for any of the α 1-subtypes. These results suggest that the α 1A-subtype plays a determining role in preventing lethality induced by noradrenaline in the rats, and that this activity is unrelated

to the hypotensive effect of the compds., which cannot be clearly correlated with affinity for a particular α 1-adrenoceptor subtype.

IT 19216-56-9, Prazosin 106133-20-4,

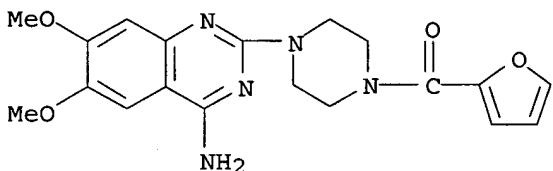
Tamsulosin

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(antagonism to noradrenaline-induced lethality relation to affinity for α 1A-adrenoceptor subtype)

RN 19216-56-9 HCPLUS

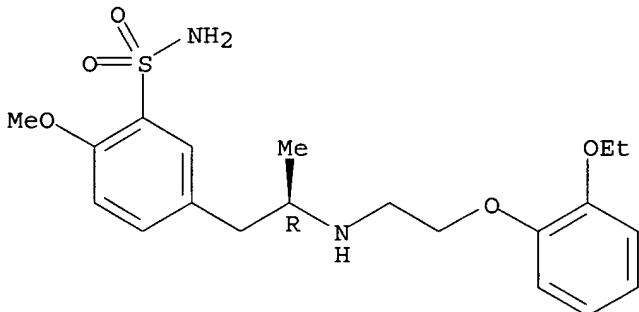
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[(2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 41 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:594633 HCPLUS

DOCUMENT NUMBER: 127:262700

TITLE: Preparation of piperazines as 5-HT1A receptor antagonists for the treatment of urinary incontinence

INVENTOR(S): Leonardi, Amedeo; Testa, Rodolfo

PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Co., Switz.; Recordati Industria Chimica e Farmaceutica S.P.A.

SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2

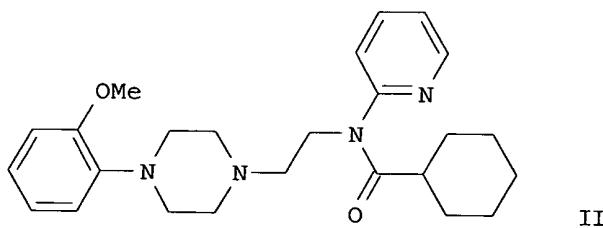
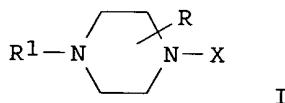
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731637	A1	19970904	WO 1997-EP897	19970225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9720932	A1	19970916	AU 1997-20932	19970225
EP 906100	A1	19990407	EP 1997-906125	19970225
EP 906100	B1	20040128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001511763	T2	20010814	JP 1997-530579	19970225
AT 258438	E	20040215	AT 1997-906125	19970225
PT 906100	T	20040630	PT 1997-906125	19970225
ES 2213205	T3	20040816	ES 1997-906125	19970225
US 5990114	A	19991123	US 1997-807338	19970228
PRIORITY APPLN. INFO.:			IT 1996-MI378	A 19960228
			WO 1997-EP897	W 19970225
OTHER SOURCE(S) :	MARPAT	127:262700		
GI				



AB The title compds. [I; R = H, lower alkyl; R1 = aryl, N-containing heteroaryl or bicyclic heteroaryl; X = (CH₂)_nCR₂R₃C(O)NR₄R₅, KN(R₆)C(O)R₇, etc.; R₂ = H, lower alkyl; R₃ = aryl, aryl(lower)alkyl; R₄ = H, C₁₋₃ alkyl; R₅ = H, C₁₋₃ alkyl, C₃₋₁₂ cycloalkyl, etc.; R₆ = monocyclic or bicyclic heteroaryl; R₇ = H, lower alkyl, cycloalkyl, etc.; K = C₂₋₄ alkylene; n = 1-2] which: (a) bind to a 5-HT_{1A} receptor with an affinity at least 10⁻⁷ M, (b) bind to a 5-HT_{1A} receptor with an affinity at least 50-fold stronger than the affinity with which compds I bind to an α₁-adrenergic receptor, and (c) exhibit 5-HT_{1A} receptor antagonist activity on both pre-synaptic and post-synaptic 5-HT_{1A} receptors, and are useful for the treatment of lower urinary tract disorders in mammals, were prepared Thus, treatment of 1-[N-(2-pyridyl)-2-aminoethyl]-4-(2-methoxyphenyl)piperazine with BuLi in THF followed by addition of cyclohexanecarbonyl chloride afforded the title compound II which showed Ki

of 0.3 nM against 5-HT1A receptor binding.

L69 ANSWER 42 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1997:407049 HCPLUS
 DOCUMENT NUMBER: 127:104105
 TITLE: Pharmacological characterization of the uroselective alpha-1 antagonist Rec 15/2739 (SB 216469): role of the alpha-1L adrenoceptor in tissue selectivity. Part II
 AUTHOR(S): Testa, R.; Guarneri, L.; Angelico, P.; Poggesi, E.; Taddei, C.; Sironi, G.; Colombo, D.; Sulpizio, A. C.; Naselsky, D. P.; Hieble, J. P.; leonardi, A.
 CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 281(3), 1284-1293
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The aim of the present work was to investigate whether or not the uroselectivity of Rec 15/2739 and several other alpha-1 adrenoceptor (α_1 -AR) antagonists observed in the anesthetized dog could be related to selectivity of these compds. for a particular alpha-1 AR subtype. The binding affinity of the tested compds. for canine prostate alpha-1 ARs and their in vitro functional affinity for the alpha-1 ARs of rabbit urethra and prostate correlated with their functional affinity for the alpha-1L AR subtype, but not with the binding affinity for recombinant animal and human alpha-1a, alpha-1b and alpha-1d AR subtypes. Similar results were obtained when the in vivo potency on urethral pressure was correlated with the affinity for the alpha-1 AR subtypes: also in this case alpha-1L AR gave the best correlation. No correlation was obtained by considering the other alpha-1 AR subtypes. The in vivo hypotensive effects observed in dog after i.v. administration of the considered compds. correlated only with the binding affinity for the animal and human alpha-1d subtype. In conclusion, the results shown in the present paper indicate that the potencies of different alpha-1 antagonists against the contractions induced by norepinephrine on tissues of the lower urinary tract of rabbits and dogs are better corelated with their affinity for the putative alpha-1L subtype than for the alpha-1a subtype. Only the compds. showing selectivity for the alpha-1L subtype vs. the alpha-1d subtype proved highly selective in vivo for the lower urinary tract vs. the vascular tissues.

L69 ANSWER 43 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1997:407048 HCPLUS
 DOCUMENT NUMBER: 127:104104
 TITLE: Pharmacological characterization of the uroselective alpha-1 antagonist Rec 15/2739 (SB 216469): role of the alpha-1L adrenoceptor in tissue selectivity. Part I
 AUTHOR(S): Leonardi, A.; Hieble, J. P.; Guarneri, L.; Naselsky, D. P.; Poggesi, E.; Sironi, G.; Sulpizio, A. C.; Testa, R.
 CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 281(3), 1272-1283
 CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

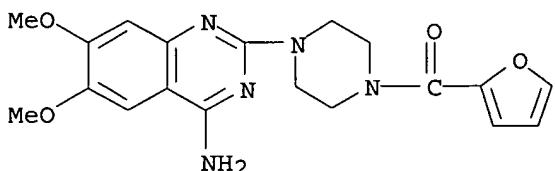
AB Alpha adrenoceptor antagonists have been convincingly shown to be beneficial in reducing both subjective and objective indexes of urethral obstruction in benign prostatic hyperplasia. Rec 15/2739 (SB 216469) is a novel alpha-1 adrenoceptor (alpha-1 AR) antagonist currently being developed for benign prostatic hyperplasia. When evaluated in radioligand binding assays with expressed animal or human alpha-1 ARs, Rec 15/2739 shows marked to moderate selectivity for the alpha-1a AR subtype. Its affinity for the recombinant alpha-2 AR subtypes or native dopaminergic D2 receptor was about 100-fold lower than that for alpha-1a AR subtype. In canine tissues, Rec 15/2739 was 20-fold more potent as an inhibitor of [³H]prazosin binding to prostate vis-a-vis aorta. Functional studies in isolated rabbit tissues also confirmed the uroselectivity of Rec 15/2739, with substantially higher affinity ($K_b = 3-3$ nM) being observed in urethra and prostate, compared with ear artery and aorta ($K_b = 20-100$ nM). The in vitro selectivity observed with Rec 15/2739 was confirmed in vivo in the anesthetized dog, comparing potency against norepinephrine- or hypogastric nerve stimulation-induced urethral contraction with its ability to reduce diastolic blood pressure. In this model, Rec 15/2739 had greater selectivity than any other alpha-1 AR antagonist examined, including terazosin and tamsulosin. Based on the low potency of prazosin and some of its structural analogs in the rabbit and dog lower urinary tract tissues, it appears that norepinephrine contrasts these tissues via activation of the alpha-1LAR. Hence this alpha-1 AR subtype, rather than the alpha-1A AR, may mediate the contraction in vivo.

L69 ANSWER 44 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1997:406096 HCPLUS
 DOCUMENT NUMBER: 127:130790
 TITLE: α -1-Adrenoceptor subtype selectivity: molecular modeling and theoretical quantitative structure-affinity relationships
 AUTHOR(S): De Benedetti, P. G.; Fanelli, F.; Menziani, M. C.; Cocchi, M.; Testa, R.; Leonardi, A.
 CORPORATE SOURCE: Dipartimento di Chimica, Universita di Modena, Modena, 41100, Italy
 SOURCE: Bioorganic & Medicinal Chemistry (1997), 5(5), 809-816
 CODEN: BMECEP; ISSN: 0968-0896
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB This study constitutes a preliminary rationalization, at the mol. level, of antagonist selectivity towards the three cloned α 1-adrenergic receptor (α 1-AR) subtypes. Mol. dynamics simulations allowed a structural/dynamics anal. of the seven α -helix-bundle models of the bovine α 1a-, hamster α 1b-, and rat α 1d-AR subtypes. The results showed that the transmembrane domains of these subtypes have different dynamic behaviors and different topogs. of the binding sites, which are mainly constituted by conserved residues. In particular, the α 1a-AR binding site is more flexible and topog. different with respect to the other two subtypes. The results of the theor. structural/dynamics anal. of the isolated receptors are consistent with the binding affinities of the 16 antagonists tested towards the three cloned α 1-AR subtypes. Moreover, the theor. quant. structure-affinity relationships obtained from the antagonist-receptor interaction models further corroborate the hypothesis that selectivity towards one preferential subtype is mainly modulated by receptor and/or

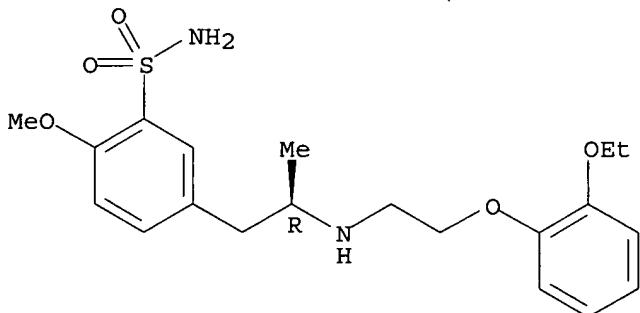
ligand distortion energies. In other words, subtype selectivity seems to be mainly guided by the dynamic complementarity (induced fit) between ligand and receptor. On the basis of the quant. models presented it is possible to predict both affinities and selectivities of putative α 1-AR ligands as well as to estimate the theor. α 1-AR subtype affinities and selectivities of existing antagonists.

IT 19216-56-9, Prazosin 106133-20-4,
Tamsulosin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. modeling and QSAR of α 1-Adrenoceptor subtype selectivity)
RN 19216-56-9 HCPLUS
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-
(9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS
CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



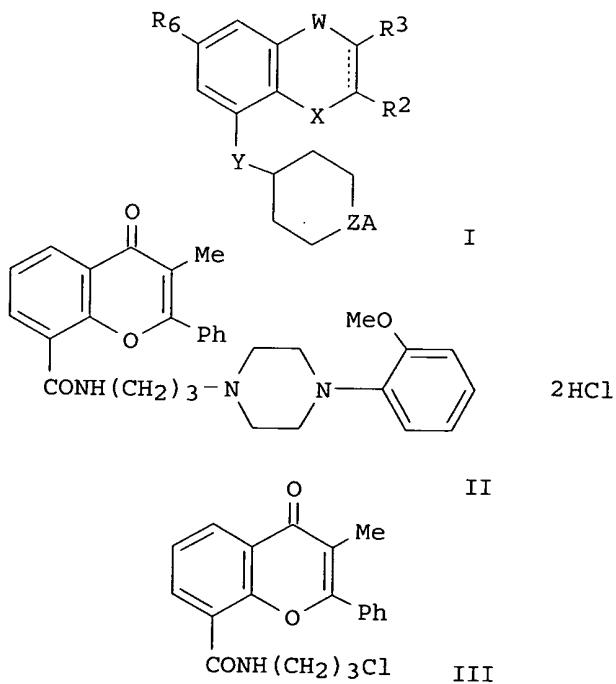
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 45 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:169157 HCPLUS
DOCUMENT NUMBER: 126:225315
TITLE: Bicyclic heterocyclic derivatives having α 1-adrenergic and 5HT1A serotonergic activities
INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo;
Testa, Rodolfo
PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company,
Switz.
SOURCE: U.S., 84 pp., Cont.-in-part of U.S. 5,474,994.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5605896	A	19970225	US 1994-299188	19940831
US 5403842	A	19950404	US 1992-888775	19920526
AU 9336296	A1	19930913	AU 1993-36296	19930223
RO 112111	B3	19970530	RO 1994-1404	19930223
PL 175556	B1	19990129	PL 1993-304889	19930223
RU 2128656	C1	19990410	RU 1994-43324	19930223
SK 280143	B6	19990910	SK 1994-1007	19930223
ZA 9301278	A	19931118	ZA 1993-1278	19930224
LT 3038	B	19940925	LT 1993-354	19930224
CN 1079738	A	19931222	CN 1993-105852	19930526
CN 1040434	B	19981028		
US 5474994	A	19951212	US 1993-67861	19930526
FI 9403876	A	19940823	FI 1994-3876	19940823
NO 9403140	A	19940825	NO 1994-3140	19940825
PRIORITY APPLN. INFO.:			IT 1992-MI408	A 19920225
			US 1992-888775	A2 19920526
			US 1993-67861	A2 19930526
			EP 1993-301264	A 19930222
			WO 1993-EP420	A 19930223

OTHER SOURCE(S) : MARPAT 126:225315
GI



AB Bicyclic heterocyclic derivs., such as I [X = N, O, S; W = C(O), C(S), CH(OH), bond; R2 = H, optionally substituted alkyl, alkenyl, alkynyl, carbocycle, heterocycle; R3 = alkyl, hydroxalkyl, Ph, OH, alkoxy, alkoxyalkyl; R6 = H, halogen, NO2, NH2, AcNH, mono-, dialkylamino, CN, OH,

alkoxy, alkyl; Y = CO, CO₂, CONH, CH(OH), CH:CH, CH:CHCO₂, CH:CHCONH, CH₂NH, CH₂NHCO, CH₂NHSO₂, CH₂O, CH₂S, NH, NHCO, NHCONH, NHSO₂, O, S, SO₂NH, CONHO, CSNH, NHCO₂, COS, CONH(CH₂)_m, m = 1-6; Z = N, A = (un)substituted Ph, pyrimidinyl, 1,4-benzodioxan-8-yl, benzopyran-8-yl, benzofuran-7-yl, dihydrobenzopyran-8-yl; Z = CH₂N; Z = CH, A = one or two Ph, 4-FC₆H₄CO, 2-oxo-1-benzimidazolinyl, (CH₂)_nOA, n = 0-2], and their pharmaceutically acceptable salts useful as α 1-adrenergic and 5HT1A serotonergic agents for the treatment of hypertension, urethral and lower urinary tract contractions, and other disorders are described. Thus, benzopyran II was prepared by heating 1-(2-methoxyphenyl)piperazine with benzopyran III at 180° for 5 h. II had IC₅₀ = 29 nM for α 1-adrenergic receptor binding, IC₅₀ = 9 nM for 5HT1A receptor binding, ED₂₅ = 45 μ g/kg i.v. hypotensive effect and ED₂₅ = 1.4 μ g/kg in Na-induced urethral contractility assays.

L69 ANSWER 46 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:628629 HCPLUS

DOCUMENT NUMBER: 126:14314

TITLE: Synthesis and Biological Profile of the Enantiomers of [4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-cis-octahydroquinoxalin-1-yl]furan-2-ylmethanone (cyclazosin), a Potent Competitive α 1B-Adrenoceptor Antagonist

AUTHOR(S): Giardina, Dario; Crucianelli, Mauro; Romanelli, Roberta; Leonardi, Amedeo; Poggesi, Elena; Melchiorre, Carlo

CORPORATE SOURCE: Department of Chemical Sciences, University of Camerino, Camerino, 62032, Italy

SOURCE: Journal of Medicinal Chemistry (1996), 39(23), 4602-4607

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The enantiomers of [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-cis-octahydroquinoxalin-1-yl]furan-2-ylmethanone (cyclazosin) (I) were synthesized from the chiral furan-2-yl(cis-octahydroquinoxalin-1-yl)methanone derivs., which were obtained by resolution of the racemic amine with (S)-(+) and (R)(-)mandelic acid. The binding profile of the enantiomers of I was assessed at α 1-, α 2-, D₂, and 5-HT1A receptors as well as at native α 1A- and α 1B- and cloned α 1a-, α 1b-, and α 1d-adrenoceptor subtypes in comparison with prazosin, spiperone, and AH11110A. (+)-I displayed a 40-90-fold selectivity for the α 1B(α 1b)-adrenoceptor relative to α 1A(α 1a) and α 1d subtypes. A significant enantioselectivity was observed at the α 1A(α 1a)-adrenoceptor and particularly at α 1d-adrenoceptors since (-)-I was 11-14- and 47-fold, resp., more potent than (+)-I. Furthermore the enantiomer (+)-I displayed selectivities of 1100-, 19000-, and 12000-fold in binding to α 1b-adrenoceptors relative to α 2-adrenoceptors and 5-HT1A and D₂ receptors. These results indicate that (+)-I, [(+)-cyclazosin] is the most potent and selective ligand for the α 1B-adrenoceptor subtype so far described and may be a valuable tool in the characterization of α 1-adrenoceptor subtypes.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 47 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:591757 HCPLUS

DOCUMENT NUMBER: 125:293060

TITLE: $\alpha 1$ -Adrenoceptors: Subtype- and organ-selectivity of different agents
AUTHOR(S): Leonardi, A.; Testa, R.; Motta, G.; Benedetti, P. G. De; Hieble, P.; Giardina, D.
CORPORATE SOURCE: R and D Division Recordati S.p.A., Milan, 20148, Italy
SOURCE: Pharmacochemistry Library (1996), 24 (Perspectives in Receptor Research), 135-152
PUBLISHER: CODEN: PHLIDQ; ISSN: 0165-7208 Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 79 refs., on the $\alpha 1$ -adrenergic receptor subtype selectivity of known and novel $\alpha 1$ -adrenergic receptor antagonists, based on radioreceptor binding study results.

L69 ANSWER 48 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:375641 HCPLUS
DOCUMENT NUMBER: 125:49151
TITLE: Functional antagonistic activity of Rec 15/2739, a novel alpha-1 antagonist selective for the lower urinary tract, on noradrenaline-induced contraction of human prostate and mesenteric artery
AUTHOR(S): Testa, Rodolfo; Guarneri, Luciano; Taddei, Carlo; Poggesi, Elena; Angelico, Patrizia; Sartani, Abraham; Leonardi, Amedeo; Gofrit, Ofer N.; Meretyk, Shimon; et al.
CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati S.p.A., Milan, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 277(3), 1237-1246
PUBLISHER: CODEN: JPETAB; ISSN: 0022-3565 Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to compare with known reference stds. the functional in vitro alpha-1 antagonistic activity of Rec 15/2739 on noradrenaline-induced contractions of human prostate and mesenteric artery. We also characterized these tissues with regard to the alpha-1 adrenoceptor subtypes present. Comparing the apparent pKB values revealed Rec 15/2739 to be one of the most potent compds. acting on the prostate. Its potency was slightly lower than that of tamsulosin and was higher than the potencies of prazosin, terazosin and 5-methylurapidil. On the mesenteric artery, tamsulosin was the most potent compound. Comparing the results from the functional studies with those obtained from radioreceptor binding studies, we found that the potency (pKB value) in inhibiting the contraction of prostatic tissue showed a close and significant correlation with the affinity for native and recombinant alpha-1A adrenoceptors. No significant correlation was found with affinity for either the native or the recombinant alpha-1B adrenoceptor subtype, or for recombinant alpha-1d receptors. Similar results were obtained for mesenteric artery. To characterize further the alpha-1 adrenoceptor subtypes present in the examined tissues, we investigated the functional effects of chloroethylclonidine, an alpha-1B-D subtypes selective alpha-1 adrenoceptor irreversible antagonist, and those of nifedipine, which antagonizes the extracellular calcium influx primarily mediated by alpha-1A adrenoceptor stimulation. The results indicate the presence of both chloroethylclonidine-sensitive and -insensitive alpha-1 adrenoceptor subtypes in the human prostate, whereas in mesenteric artery the alpha-1A subtype seems to be present exclusively. The possibility that the functionally relevant alpha-1 adrenoceptor

subtype could be classified as alpha-1L in both tissues should also be considered.

L69 ANSWER 49 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1996:260102 HCPLUS
 DOCUMENT NUMBER: 124:307070
 TITLE: Hemodynamic effects of lercanidipine in anesthetized open-chest dogs
 AUTHOR(S): Sironi, Giorgio; Montagna, Ernesto; Greto, Luigi;
 Leonardi, Amedo; Testa, Rodolfo
 CORPORATE SOURCE: Pharmaceutical R&D Div., Recordati S.p.A., Milan,
 Italy
 SOURCE: Arzneimittel-Forschung (1996), 46(3), 256-61
 CODEN: ARZNAD; ISSN: 0004-4172
 PUBLISHER: Cantor
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In this study, the hemodynamic effects of lercanidipine (CAS 132866-11-6, Rec 15/2375) in anesthetized open-chest dogs were investigated in comparison with nitrendipine. I.v. administered lercanidipine induced a dose-related, long lasting reduction in systemic and coronary vascular resistances, with concomitant decrease in arterial blood pressure and increase in coronary blood flow. The hypotensive ED₂₅ was 6.1 µg/kg and 4.2 µg/kg (decrease of mean blood pressure and of total peripheral resistances, resp.) and the ED₅₀ on coronary vasodilation, 4.8 µg/kg and 7.8 µg/kg (increase of coronary blood flow and decrease in coronary vascular resistances, resp.). The time-course of the hemodynamic effects was investigated after administration of 5 µg/kg. A slow onset of hemodynamic vasodilation and long-lasting activity were observed, since peak effects on mean blood pressure and coronary blood flow occurred at 20 and 30 min after the administration, resp., and the effects on systemic and coronary resistances were still significant at 30 and 150 min after administration, resp.

L69 ANSWER 50 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1996:234275 HCPLUS
 DOCUMENT NUMBER: 124:307311
 TITLE: Rec 15/2739 (SB 216469): a novel prostate selective α₁-adrenoceptor antagonist
 AUTHOR(S): Testa, R.; Taddei, C.; Poggesi, E.
 ; Destefani, C.; Cotecchia, S.; Hieble, J. P.;
 Sulpizio, A. C.; Naselsky, D.; Bergsma, D.; et al.
 CORPORATE SOURCE: Res. Development Div., Recordati S.p.A., Milan, 21048,
 Italy
 SOURCE: Pharmacology Communications (1995), 6(1-3), 79-86
 CODEN: PCMME9; ISSN: 1060-4456
 PUBLISHER: Harwood
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Rec 15/2739 (SB 216469) is a novel agent having potent α₁-adrenoceptor antagonist activity. Rec 15/2739 selectively inhibited [³H] prazosin binding to tissue homogenates of native α_{1A}- and α_{1C}-adrenoceptors and to recombinant α_{1C}-adrenoceptors. Rec 15/2739 also produced potent inhibition of [³H] prazosin binding to human prostate membranes ($K_i = 2.0 \text{ nM}$). In functional studies using rabbit tissues, Rec 15.2739 was 39 fold more potent in prostatic strips ($K_B = 2.7 \text{ nM}$) than in segments of ear artery ($K_B = 106 \text{ nM}$). This degree of functional selectivity was not observed with any of the other α₁-adrenoceptor antagonist tested. The α₁-adrenoceptor antagonists currently utilized for the therapy of

benign prostatic hyperplasia (BPH) are often associated with side-effects attributable to blockade of vascular α_1 -adrenoceptors. Hence, Rec 15/2739 may offer a therapeutic advantage, since it may be possible to block prostatic α_1 -adrenoceptors with this drug at a dose not influencing the vascular α_1 -adrenoceptors.

L69 ANSWER 51 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1996:174557 HCAPLUS
 DOCUMENT NUMBER: 124:250406
 TITLE: Pharmacological in vitro studies of the new
 1,4-dihydropyridine calcium antagonist lercanidipine
 AUTHOR(S): Guarneri, Luciano; Angelico, Patrizia; Ibba, Marina;
 Poggesi, Elena; Taddei, Carlo; Leonardi,
 Amedeo; Testa, Rodolfo
 CORPORATE SOURCE: Pharmaceutical R&D Division, Recordati S.p.A., Milan,
 Italy
 SOURCE: Arzneimittel-Forschung (1996), 46(1), 15-24
 CODEN: ARZNAD; ISSN: 0004-4172
 PUBLISHER: Cantor
 DOCUMENT TYPE: Journal
 LANGUAGE: English

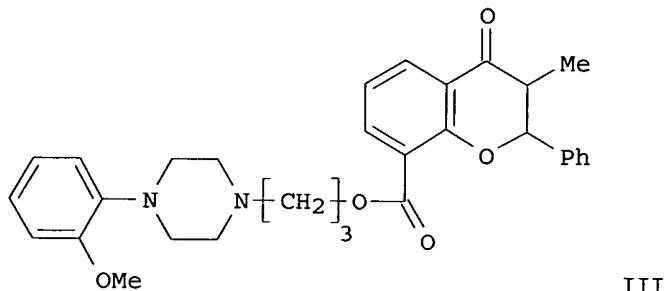
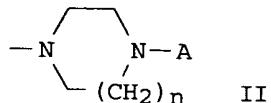
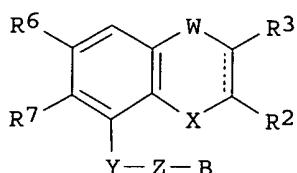
AB The present studies were undertaken to examine the in vitro calcium antagonistic properties of lercanidipine (CAS 132866-11-6, Rec 15/2375) in vascular and non-vascular tissues, as well as its binding profile and in particular its affinity to the calcium channel binding sites. Lercanidipine proved to be endowed with high affinity for the hydropyridine subunit of the L-type calcium channel, where it was much more potent than on the other receptors tested. The nature of the interaction of lercanidipine with the calcium channel appears competitive, as evidenced by a progressive increase in the apparent K_d of the ligand with no change in B_{max} . The performed functional in vitro studies in isolated vascular and cardiac tissues demonstrated that lercanidipine has a slower onset and offset of calcium antagonistic activity compared with other calcium antagonists. The time-course of inhibition of vascular smooth muscle contraction showed substantial differences after addition of lercanidipine with regard to the other calcium antagonists tested (nitrendipine and amlodipine). On repeated washing of rat aorta to remove the drugs from the preparation, the effects of nitrendipine disappeared rapidly. After amlodipine incubation, contractility of the tissue was still impaired after 6 h washout with the highest concns. tested, but completely recovered in 1-3 h after washout of the lowest concentration. On the contrary, the preps. incubated with lercanidipine showed a decrease in contractility that reached the maximum 1 to 3 h after the removal of the compound from the bath at all the active concns. tested. The functional calcium antagonistic activity of lercanidipine showed a decrease in contractility that reached the maximum 1 to 3 h after the removal of the compound from the bath at all the active concns. tested. The functional calcium antagonistic activity of lercanidipine showed a decrease in contractility that reached the maximum 1 to 3 h after the removal of the compound from the bath at all the active concns. tested. The functional calcium antagonistic activity of lercanidipine was also evaluated as relaxing potency against the tonic contractions induced by preincubation of rat aorta, bladder and colon with 80 mmol/l K⁺. In rat aorta, lercanidipine proved more potent than nitrendipine. Comparing the IC₅₀ values evaluated after 3 h of contact time, lercanidipine resulted more active on the vascular tissue with potency ratios of 177 and 8.5 for aorta vs. bladder and aorta vs. colon, resp. In contrast,

nitrendipine showed about the same activity in the three tested tissues, and potency ratios of 2.0 and 0.8 for aorta vs. bladder and aorta vs. colon were calculated. In rat aortic strips maintained during the incubation with lercanidipine at different degrees of depolarization, the functional calcium antagonistic activity markedly increased by raising the tissue depolarization, the functional calcium antagonistic activity markedly increased by raising the tissue depolarization and the potency ratio between the IC₅₀ values evaluated at 5 and 100 mmol/l K⁺ resulted 138. Nitrendipine provided very similar results, whereas nifedipine activity did not seem to be affected by raising the tissue depolarization. The neg. inotropic effects of lercanidipine on normally and partially depolarized rabbit ventricular strips, as well as in guinea-pig atria, were negligible in comparison to its effects on vasculature. On the whole these characteristics suggest a slow onset of action and long duration of effects also after in vivo administration. In addition, the unique vascular selectivity of lercanidipine implies that the therapeutically desirable vasodilator activity is not or scarcely associated with a decrease in cardiac contractile force.

L69 ANSWER 52 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1996:35000 HCAPLUS
 DOCUMENT NUMBER: 124:232248
 TITLE: Benzopyran derivatives having affinity for α₁-adrenergic and 5HT1A-serotonergic receptors
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo;
 Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati S.A., Chemical and Pharmaceutical Company,
 Switz.
 SOURCE: U.S., 37 pp. Cont.-in-part of U.S. 5,403,842.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5474994	A	19951212	US 1993-67861	19930526
US 5403842	A	19950404	US 1992-888775	19920526
EP 558245	A1	19930901	EP 1993-301264	19930222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AU 9336296	A1	19930913	AU 1993-36296	19930223
RO 112111	B3	19970530	RO 1994-1404	19930223
PL 175556	B1	19990129	PL 1993-304889	19930223
SK 280143	B6	19990910	SK 1994-1007	19930223
CN 1079738	A	19931222	CN 1993-105852	19930526
CN 1040434	B	19981028		
FI 9403876	A	19940823	FI 1994-3876	19940823
NO 9403140	A	19940825	NO 1994-3140	19940825
US 5605896	A	19970225	US 1994-299188	19940831
PRIORITY APPLN. INFO.:			US 1992-888775	A2 19920526
			EP 1993-301264	A 19930222
			IT 1992-MI408	A 19920225
			WO 1993-EP420	A 19930223
			US 1993-67861	A2 19930526

OTHER SOURCE(S): MARPAT 124:232248
 GI



AB This invention provides bicyclic heterocyclic derivs. I wherein the dotted line represents a single or double bond; X represents a nitrogen, oxygen or sulfur atom, or an amino or alkylamino group, a sulfinyl or sulfonyl group; W represents a carbonyl, thiocarbonyl, hydroxymethylene, or a methylene group or a bond; or when X is nitrogen and W is a methine, the fused rings represent a quinoline; R2 represents, e.g., a hydrogen atom or an alkyl, alkenyl, alkynyl, carbocyclic or heterocyclic group, each of which groups may optionally be substituted; or R2 itself represents a trifluoromethyl or an aroyl group; R3 represents a hydrogen atom or an alkyl, hydroxylalkyl, alkyl-O-R4 Ph, hydroxy, or O-R4, wherein R4 represents an alkyl group optionally substituted with an aryl group; R6 represents a hydrogen or halogen atom or a nitro, amino, acylamino, alkylsulfonylamino, alkylamino, dialkylamino, cyano, hydroxy, alkoxy or alkyl group; R7 represents a hydrogen atom or an alkoxy group; Y = e.g., CO, COO, CONH; Z represents a linear or branched chain alkylene group having from 1 to 6 carbon atoms and optionally having one hydroxy substituent; B = e.g., II, n = 1 or 2, A = substituted Ph, 2-pyrimidinyl; and their pharmaceutically acceptable salts useful for the treatment of hypertension, urethral and lower urinary tract contractions, and other disorders. The compds. are also useful for binding α_1 -adrenergic and 5HT1A serotonergic receptors, in vitro or in vivo. Thus, e.g., esterification of 8-carboxy-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran with 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine followed by HCl treatment afforded 8-{3-[4-(2-methoxyphenyl)-1-piperazinyl]propoxycarbonyl}-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran dihydrochloride (III.2HCl) which exhibited IC50's of 20 and 19 nM, resp., for α_1 and 5-HT1A receptor binding. Data were also presented for the effect of I on K⁺ stimulation of rat bladder strips, and on urethral contractions and blood pressure in dogs.

L69 ANSWER 53 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:995217 HCPLUS

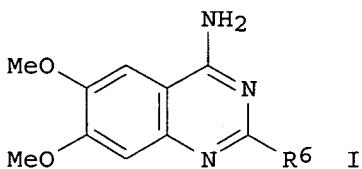
DOCUMENT NUMBER: 124:117340

TITLE: Preparation of 4-amino-2-piperazinoquinazolines and analogs as α_1 - adrenergic antagonists

INVENTOR(S): Leonardini, Amedeo; Motta, Gianni; Boi, Carlo;
 Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati S.A. Chemical and Pharmaceutical Co., Switz.
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9525726	A1	19950928	WO 1995-EP1001	19950317
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9518948	A1	19951009	AU 1995-18948	19950317
ZA 9502208	A	19951228	ZA 1995-2208	19950317
EP 750614	A1	19970102	EP 1995-911342	19950317
EP 750614	B1	20010523		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE JP 09511238	T2	19971111	JP 1995-524370	19950317
JP 3683911	B2	20050817		
IL 113024	A1	20000726	IL 1995-113024	19950317
ES 2158938	T3	20010916	ES 1995-911342	19950317
PT 750614	T	20011031	PT 1995-911342	19950317
TW 416951	B	20010101	TW 1995-84105132	19950523
US 5798362	A	19980825	US 1996-716160	19960917
GR 3036443	T3	20011130	GR 2001-401292	20010823
PRIORITY APPLN. INFO.:			IT 1994-MI506	A 19940318
			WO 1995-EP1001	W 19950317

OTHER SOURCE(S): MARPAT 124:117340
 GI



AB Title compds. [I; R₆ = Z₁Z₂(CR₁R₂)_mR, NMeZR₇, 4,4-diphenylpiperidino, etc.; R = aryl(oxy), diarylmethyl, aroyl, etc.; R₁,R₂ = H, alkyl; R₇ = Ph, CHPh₂, 4-(2-methoxyphenyl)piperazino; Z = alkylene; Z₁ = 1,4-piperazinylene; Z₂ = bond, O, CO, CONH; m = 0-4; n = 0 or 1] were prepared. Thus, I (R₆ = piperazino) was amidated by PhCOCH₂CO₂H to give I (R₆ = Z₁COCH₂COPh, Z₁ = 1,4-piperazinylene) which had ED₂₅ for blood pressure reduction of 56μg/kg i.v. in normotensed rats and 2.42mg/kg orally in spontaneously hypertensive rats.

L69 ANSWER 54 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:961873 HCAPLUS

DOCUMENT NUMBER: 124:76223

TITLE: Receptor binding profile of cyclazosin, a new

AUTHOR(S) : **α 1B-adrenoceptor antagonist**
 Giardina, Dario; Crucianelli, Mauro; Melchiorre, Carlo; Taddei, Carlo; Testa, Rodolfo

CORPORATE SOURCE: Department of Chemical Sciences, University of Camerino, Via S. Agostino 1, Camerino (MC), 62032, Italy

SOURCE: European Journal of Pharmacology (1995), 287(1), 13-16
 CODEN: EJPRAZ; ISSN: 0014-2999

PUBLISHER: Elsevier

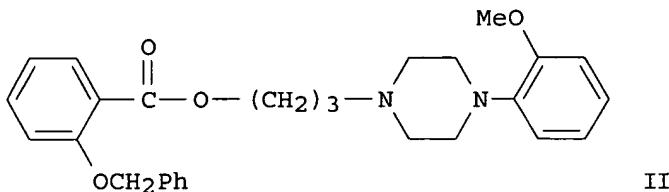
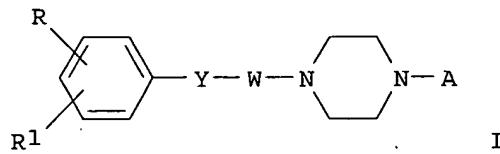
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The binding profile of cyclazosin, a new prazosin-related α 1-adrenoceptor antagonist, at α 1-, α 2-adrenoceptors, dopamine D2 and 5-HT1A receptors was compared to that of 5-methylurapidil, spiperone, risperidone and other prazosin-related ligands. In addition, cyclazosin was investigated at native and cloned α 1-adrenoceptor subtypes. Cyclazosin showed high specificity for α 1-adrenoceptors and a 10-15-fold selectivity for α 1B (α 1b)-adrenoceptors with respect to the α 1A (α 1a) subtype (pKi values of 9.23-9.57 and 8.18-8.41, resp.). However, it failed to discriminate between cloned α 1b and α 1d-adrenoceptors (pKi values of 9.23 and 9.28, resp.).

L69 ANSWER 55 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:807948 HCPLUS
 DOCUMENT NUMBER: 123:228215
 TITLE: Piperazine derivatives as α 1A-adrenergic receptor antagonists
 INVENTOR(S) : Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S) : Recordati Industria Chimica e Farmaceutica S.p.A., Italy; Recordati S.A., Chemical and Pharmaceutical Co.
 SOURCE: PCT Int. Appl., 60 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9504049	A1	19950209	WO 1994-EP2437	19940722
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2168443	AA	19950209	CA 1994-2168443	19940722
AU 9475323	A1	19950228	AU 1994-75323	19940722
AU 680037	B2	19970717		
EP 711288	A1	19960515	EP 1994-925382	19940722
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1132508	A	19961002	CN 1994-193622	19940722
JP 09500883	T2	19970128	JP 1994-505546	19940722
ZA 9405625	A	19950307	ZA 1994-5625	19940729
NO 9600371	A	19960329	NO 1996-371	19960129
PRIORITY APPLN. INFO.:			IT 1993-MI1717	A 19930730
			WO 1994-EP2437	W 19940722
OTHER SOURCE(S) : GI		CASREACT 123:228215; MARPAT 123:228215		



AB Title compds. I are disclosed [in which Y = bond, SOn, NR2, NR2CO, PO(OEt)NH, NHCONH, CO, SO2NR2, (CH2)nCOO, (CH2)nCONR2; W = C2-6 alkylene; A = substituted Ph, or a benzofuran or benzodioxan group; R and R1 have many values, but R is preferably bulky; with provisos]. I and their prodrugs, enantiomers, diastereoisomers, N-oxides, and pharmaceutically acceptable salts block α 1A-adrenergic receptors, and are useful for preventing contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure. Because of their generally low toxicity, less selective I at higher dosages may also be useful as antihypertensives. For example, O-alkylation of 2-benzyloxybenzoic acid with 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine in DMF in the presence of K2CO3 at 80° gave title compound II, isolated as its di-HCl salt (III). Compared to prazosin (IV), III had slightly lower α 1A-adrenoceptor affinity and comparable oral toxicity in mice, but in expts. on urethral contractility and blood pressure in dogs, III showed higher selectivity for urethral activity, with a blood pressure/urethral ED ratio of 6.7, vs. 1.8 for IV and 2.6 for urapidil.

L69 ANSWER 56 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:760152 HCAPLUS

DOCUMENT NUMBER: 123:161416

TITLE: The α 1d-adrenoceptor subtype is involved in the noradrenaline-induced contractions of rat aorta

AUTHOR(S): Testa, Rodolfo; Destefani, Carla; Guarneri, Luciano; Poggesi, Elena; Simonazzi, Iris; Taddei, Carlo; Leonardi, Amedeo

CORPORATE SOURCE: Research & Development Department, RECORDATI, Milan, 20148, Italy

SOURCE: Life Sciences (1995), 57(13), PL159-PL163
CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pA₂ value of several α 1-adrenoceptor antagonists on noradrenaline-induced contractions of rat aorta, and their affinity for the cloned α 1a-, α 1b- and α 1d-adrenoceptor subtypes were evaluated. Selective or moderately selective α 1d-, partially selective α 1b- and non-subtype-selective α 1-adrenoceptors antagonists were included in the study. The potency of these compds. on

rat aorta was well correlated with the affinity observed for the α_{1d} -adrenoceptor subtype. A poor correlation was found for the α_{1b} - and α_{1a} -subtypes. These results suggest that the α_{1d} -subtype plays a determining role in rat aorta contractions induced by noradrenaline.

L69 ANSWER 57 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:396416 HCPLUS
 DOCUMENT NUMBER: 122:152053
 TITLE: Mediation of noradrenaline-induced contractions of rat aorta by the α_{1B} -adrenoceptor subtype
 AUTHOR(S): Testa, R.; Guarneri, L.; Poggesi, E.
 ; Simonazzi, I.; Taddei, C.; Leonardi, A.
 CORPORATE SOURCE: Res. Dev. Div., Recordati S.p.A., Milan, 20148, Italy
 SOURCE: British Journal of Pharmacology (1995), 114(4), 745-50
 CODEN: BJPCBM; ISSN: 0007-1188
 PUBLISHER: Stockton
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The subtypes of α_1 -adrenoceptor mediating contractions to exogenous noradrenaline (NA) in rat aorta have been examined in both biochem. and functional studies. Incubation of rat aortic membranes with the irreversible α_{1B} -adrenoceptor antagonist, chloroethylclonidine (CEC: 10 μ M) did not change the KD of [3 H]- prazosin binding in comparison to untreated membranes, but reduced by 88% the total number of binding sites (B_{max}). Contractions of rat aortic strips to NA after CEC (50 μ M) for 30 min incubation followed by repetitive washing, showed a marked shift in the potency of NA and a partial reduction in the maximum response. The residual contractions to NA after CEC incubation were not affected by prazosin (10 nM). The competitive antagonists prazosin, terazosin, (R)-YM-12617, phentolamine, 5-methylurapidil and spiperone inhibited contractions to NA with estimated pA₂ values of 9.85, 8.54, 9.34, 7.71, 7.64 and 8.41, resp. The affinity of the same antagonists for the α_{1A} - and α_{1B} -adrenoceptors was evaluated by utilizing membranes from rat hippocampus pretreated with CEC, and rat liver, resp. 5-Methylurapidil and phentolamine were confirmed as selective for the α_{1A} -adrenoceptors, whereas spiperone was α_{1B} -selective. A significant correlation was found between the pA₂ values of the α_1 -adrenoceptor antagonists tested and their affinity for the α_{1B} -adrenoceptor subtype, but not for the α_{1A} subtype. In conclusion, these findings indicate that in rat aorta most of the contraction is mediated by α_{1B} -adrenoceptors, and that the potency (pA₂) of an antagonist in this tissue should be related to its antagonistic effect on this subtype of the α_1 -adrenoceptor population.

L69 ANSWER 58 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1995:253820 HCPLUS
 DOCUMENT NUMBER: 122:23985
 TITLE: The heuristic-direct approach to theoretical quantitative structure-activity relationship analysis of α_1 -adrenoceptor ligands
 AUTHOR(S): Fanelli, F.; Menziani, M. C.; Cocchi, M.; Leonardi, A.; De Benedetti, P. G.
 CORPORATE SOURCE: Dipartimento di Chimica, Universita di Modena, V. Campi 183, Modena, 41100, Italy
 SOURCE: THEOCHEM (1994), 120(3), 265-76
 CODEN: THEODJ; ISSN: 0166-1280
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal

LANGUAGE: English

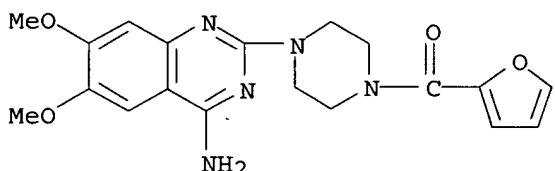
AB The heuristic-direct quant. structure-activity relation approach was applied to 15 non-congeneric α 1-adrenergic receptor (α 1-AR) ligands interacting with the rat α 1A/D-AR subtype. The good linear correlations, which have been obtained between calculated binding energies and the pharmacol. affinities, allow one to predict the pharmacol. affinity of new ligands. Moreover, according to the α 1A/D-receptor model proposed, it has been possible to speculate on the amino acid residues which are mainly involved in the interaction with the ligands. This novel procedure constitutes a powerful tool for the design of new selective leads based on explicit intermol. interactions and for suggesting site-directed mutagenesis studies, to give, interactively, further support and improvement to the predictive and interpretative aspects of the model.

IT 19216-56-9, Prazosin 74191-85-8,
Doxazosin 106133-20-4 106138-88-9

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(heuristic-direct approach to theor. QSAR anal. of α 1-adrenoceptor ligands)

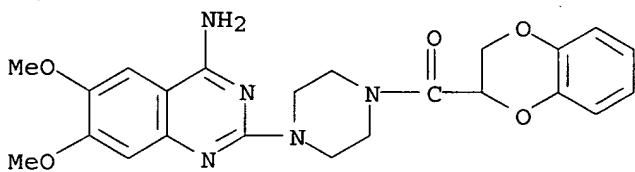
RN 19216-56-9 HCPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 74191-85-8 HCPLUS

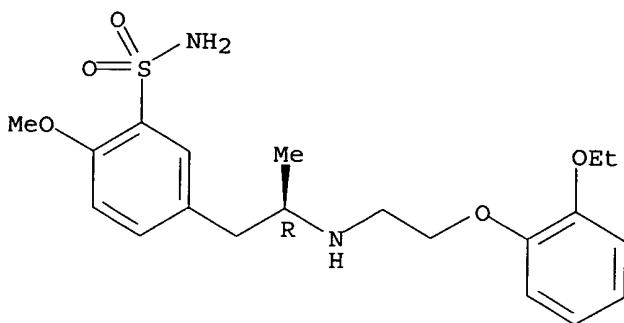
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-(9CI) (CA INDEX NAME)



RN 106133-20-4 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-(9CI) (CA INDEX NAME)

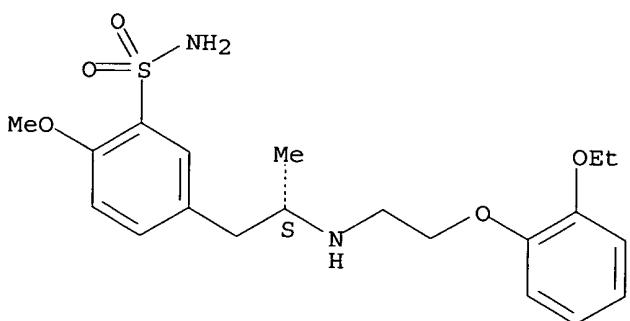
Absolute stereochemistry. Rotation (-).



RN 106138-88-9 HCPLUS

CN Benzenesulfonamide, 5-[(2S)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L69 ANSWER 59 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:569448 HCPLUS

DOCUMENT NUMBER: 121:169448

TITLE: A review of flavoxate: Pharmacology and mechanism of action

AUTHOR(S): Guarneri, Luciano; Robinson, Elisabeth; Testa, Rodolfo

CORPORATE SOURCE: Research & Development Division, Recordati S.p.A., Milan, 20148, Italy

SOURCE: Drugs of Today (1994), 30(2), 91-8
CODEN: MDACAP; ISSN: 0025-7656DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 50 refs. Preclin. pharmacol. studies show that flavoxate has in vitro antispasmodic activity on the bladder, with no anticholinergic properties. Its calcium antagonist action, local anesthetic properties and inhibitory effects on phosphodiesterases have been demonstrated and are hypothesized to be the mechanisms responsible for its spasmolytic activity on the urinary bladder.

In vivo studies in animal models show that flavoxate inhibits the frequency of volume-induced rhythmic bladder voiding contractions and increases bladder volume capacity without affecting the amplitude of the contractions, indicating activity on micturition center(s) and/or on bladder afferences without acting on the efferent system. Thus, flavoxate affects the transmission of the voiding impulse without impairing bladder contractility. In contrast,

anticholinergic drugs such as oxybutynin block the efferent neural postganglionic pathways, impairing all bladder contractions caused by unwanted micturition reflexes as well as by normal bladder voiding impulses. In terms of clin. importance, flavoxate, because of its mechanism of action, could be useful in alleviating the problem of residual urine in chronically treated patients, particularly in elderly persons with reduced contractility of the urinary detrusor. Furthermore, flavoxate, in contrast to anticholinergics, does not inhibit normal micturition nor aggravate the build up of residual urine. This advantage is of particular importance for patients with obstructive syndromes such as BPH, where anticholinergics are expressly contraindicated.

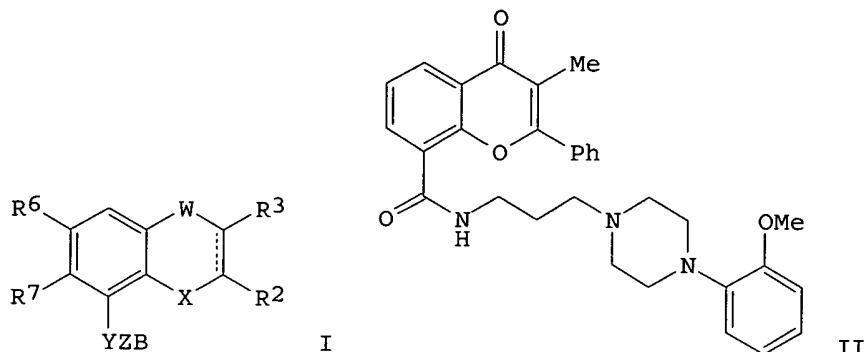
L69 ANSWER 60 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:106770 HCPLUS
 DOCUMENT NUMBER: 120:106770
 TITLE: Heterobicyclic compounds (flavoxate analogs) as antagonists of α_1 -adrenergic and 5-HT1A receptors
 INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Testa, Rodolfo
 PATENT ASSIGNEE(S): Recordati S.A. Chemical and Pharmaceutical Co., Switz.; Recordati Industria Chimica e Farmaceutica S.p.a.
 SOURCE: Eur. Pat. Appl., 109 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 558245	A1	19930901	EP 1993-301264	19930222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5403842	A	19950404	US 1992-888775	19920526
CA 2090156	AA	19930826	CA 1993-2090156	19930223
WO 9317007	A1	19930902	WO 1993-EP420	19930223
W: AU, BG, CA, CZ, FI, HU, KR, LK, NO, NZ, PL, RO, RU, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9336296	A1	19930913	AU 1993-36296	19930223
HU 72448	A2	19960429	HU 1994-2443	19930223
RO 112111	B3	19970530	RO 1994-1404	19930223
PL 175556	B1	19990129	PL 1993-304889	19930223
RU 2128656	C1	19990410	RU 1994-43324	19930223
SK 280143	B6	19990910	SK 1994-1007	19930223
IL 104824	A1	19991222	IL 1993-104824	19930223
AU 9333773	A1	19930826	AU 1993-33773	19930224
AU 660067	B2	19950608		
ZA 9301278	A	19931118	ZA 1993-1278	19930224
LT 3038	B	19940925	LT 1993-354	19930224
LV 10099	B	19950220	LV 1993-136	19930224
JP 06009606	A2	19940118	JP 1993-36605	19930225
TW 382628	B	20000221	TW 1993-82103988	19930520
CN 1079738	A	19931222	CN 1993-105852	19930526
CN 1040434	B	19981028		
US 5474994	A	19951212	US 1993-67861	19930526
FI 9403876	A	19940823	FI 1994-3876	19940823
NO 9403140	A	19940825	NO 1994-3140	19940825
PRIORITY APPLN. INFO.:			IT 1992-MI408	A 19920225

US 1992-888775 A 19920526
EP 1993-301264 A 19930222
WO 1993-EP420 A 19930223

OTHER SOURCE(S) : MARPAT 120:106770
GI



AB Title compds. I [dotted line = optional double bond; X = O, S, imino, alkylimino, S(O), S(O)2; W = bond, CO, C(S), CH₂, CH(OH); R₂ = H, (un)substituted alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aroyl; R₃ = H, alkyl, hydroxyalkyl, alkoxyalkyl, aralkoxyalkyl, Ph, OH, alkoxy, aralkoxy; R₆ = H, halo, NO₂, (un)substituted NH₂, cyano, OH, alkoxy, alkyl; R₇ = H, alkoxy; Y = 49 bivalent functional groups such as CO, CO₂, CONH, CH:CH, CH₂, CH₂NH, CH₂O, O, S, SO₂NH, etc.; Z = C₁₋₆ alkylene with 1 optional OH substituent; B = various complex amine-containing groups including substituted piperazines, piperidines, phenoxyalkylamines, etc.] and their prodrugs, N-oxides, and salts are claimed, with approx. 130 synthetic examples and 100 intermediate preps. For example, 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carbonyl chloride was amidated with H₂N(CH₂)₃OH, and the resulting N-(3-hydroxypropyl) amide was converted to the N-(3-chloropropyl) amide by SOC₂. Condensation of this with 1-(2-methoxyphenyl)piperazine at 180° gave title compound II. I inhibited α₁ receptor binding ([³H]- prazosin), 5-HT_{1A} receptor binding ([³H]-8-OH-DPAT), and K⁺-induced contraction of isolated rat bladder, with different I showing different degrees and combinations of activity. For example, II had IC₅₀ values of 29 nM, 9 nM, and 2.9-3.0 μM in the 3 tests, whereas flavoxate was inactive in the receptor tests and only had IC₅₀ of 13 μM in the bladder test. Some I and especially II showed high selectivity for urethral spasmolytic activity over antihypertensive activity in dogs.

L69 ANSWER 61 OF 75 HCAPLUS COPYRIGHT 2006 ACS OR STN

ACCESSION NUMBER: 1994:24175 HCABLIJS

ACCESSION NUMBER: 1994.2417
DOCUMENT NUMBER: 120:24175

DOCUMENT NUMBER: 120.24173
TITLE: Characterization of α_1 -adrenoceptor subtypes in prostate and prostatic urethra of rat, rabbit, dog and man

AUTHOR(S): Testa, Rodolfo; Guarneri, Luciano; Ibhah, M.

CORPORATE SOURCE: Tecca, Riccardo; Guarneri, Luciano; Ibla,
SOURCE: Marina; Strada, Guido; Poggesi, Elena;
Taddei, Carlo; Simonazzi, Iris; Leonardi, Amedeo
Res. Lab., Recordati S.p.A., Milan, 20148, Italy
European Journal of Pharmacology (1993), 249(3),
307-15

CODEN: EJPHAZ; ISSN: 0014-2999

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB The α 1-adrenoceptor subtypes present in the smooth muscle of urethra and prostate of different animal species, including man, were characterized by using receptor binding techniques. In prostatic urethra and prostate membranes, [³H]prazosin labeled a single population of α 1-adrenoceptors (Hill coefficient not different from unity) with a high affinity in the range 0.21-0.51 nM. The number of specific [³H] prazosin binding sites was partially affected by chloroethylclonidine only in human and rat prostate membranes, whereas this agent proved practically devoid of activity in rabbit and dog prostate membranes as well as in the prostatic urethra membranes of all the animal species examined. These findings indicate that in prostatic and urethral membranes the α 1-adrenoceptors mainly belong to the α 1A subtype. The binding results were confirmed by in vitro functional studies on noradrenaline-induced contractions of rabbit and dog urethral preps. The agonist-induced contractions were practically unaffected by preincubation of both tissues with chloroethylclonidine, but were sensitive to nifedipine. The authors found, moreover, a good correlation between the potency of different selective and non-selective α 1-adrenoceptor antagonists (WB-4101, 5-methylurapidil, phentolamine, spiperone, prazosin and urapidil) tested against the noradrenaline-induced contractions of rabbit urethra and their affinity for the α 1A-adrenoceptor subtype, no correlation with the affinity for the α 1B subtype, and a lower correlation with the affinity for the α 1C-adrenoceptor subtype.

L69 ANSWER 62 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:641204 HCPLUS

DOCUMENT NUMBER: 119:241204

TITLE: Affinity of different α 1-agonists and antagonists for the α 1-adrenoceptors of rabbit and rat liver membranes

AUTHOR(S): Taddei, Carlo; Poggesi, Elena; Leonardi, Amedeo; Testa, Rodolfo

CORPORATE SOURCE: Res. Dep., RECORDATI S.p.A., Milan, 20148, Italy

SOURCE: Life Sciences (1993), 53(12), PL177-PL181

CODEN: LIFSAK; ISSN: 0024-3205

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In membranes prepared from rabbit liver, competition with [³H] prazosin of different α 1-agonists and antagonists revealed different affinities in comparison to the result obtained on rat liver membranes, and showed a good correlation with the affinity of the same compds. for the cloned α 1c-adrenoceptor subtype. The potencies observed on rat liver membranes were well correlated with the affinity observed for the cloned α 1b-adrenoceptors. These results confirm that rabbit and rat liver membranes preps. can be utilized to evaluate the affinity of compds. for these α 1-adrenergic subtypes.

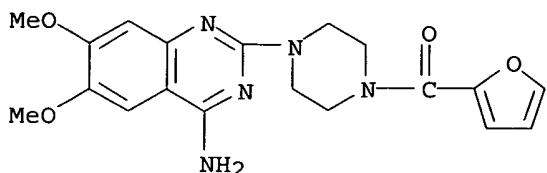
IT 19216-56-9, Prazosin 106463-17-6

RL: PRP (Properties)

(affinity of, to α 1-adrenergic receptor subtypes, in rat and rabbit liver membrane)

RN 19216-56-9 HCPLUS

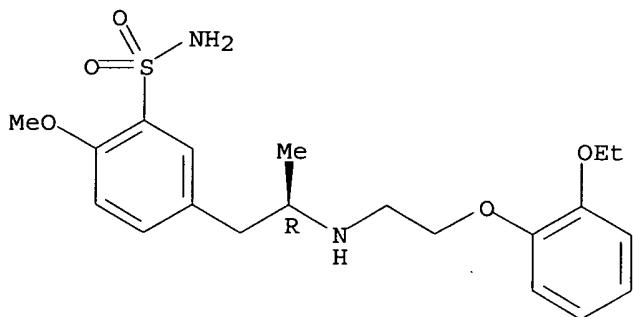
CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



RN 106463-17-6 HCPLUS

CN Benzenesulfonamide, 5-[(2R)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L69 ANSWER 63 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:420336 HCPLUS

DOCUMENT NUMBER: 119:20336

TITLE: Effects of drugs used in the therapy of detrusor hyperactivity on the volume-induced contractions of the rat urinary bladder

AUTHOR(S): Guarneri, L.; Ibba, M.; Angelico, P.; Colombo, D.; Fredella, B.; Testa, R.

CORPORATE SOURCE: Pharmacol. Dep., Recordati S.p.A., Milan, 20148, Italy

SOURCE: Pharmacological Research (1993), 27(2), 173-87

CODEN: PHMREP; ISSN: 1043-6618

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In this study, the authors examined the effects of the drugs most commonly utilized in the therapy of overactive detrusor, on the volume-induced contractions of rat urinary bladder. Anticholinergics such as propantheline bromide and emepronium bromide, as well as oxybutynin decreased the amplitude of the voiding contractions after i.v. administration in a dose-dependent way. These anticholinergics, on the other hand, generally increased the frequency of the contractions. Nifedipine dose-dependently reduced the amplitude of the contractions. Flavoxate induced a dose-related decrease in the frequency without effects on the amplitude of the peaks. Its main metabolite 3-methylflavone-8-carboxylic acid (MFCA) was inactive after i.v. administration. Terodilane was active on the amplitude and apparently on the frequency of the voiding contractions. The

α -adrenoceptor antagonist prazosin, as well as indomethacin, inhibited only the frequency of the voiding contractions. All the drugs active in reducing the frequency of the voiding contractions after i.v. administration, proved effective also after intracerebroventricular (i.c.v.) injection. The model of the volume-induced contractions of rat urinary bladder, seems to be a useful tool to evaluate in vivo the effects of a compound on the bladder, allowing the possibility of distinguishing among antimuscarinics and calcium antagonists, which peripherally decrease bladder contractility, and other drugs inducing a decrease in the frequency of the voiding reflex acting on the micturition centers in the CNS.

IT 5633-20-5, Oxybutynin 19216-56-9,

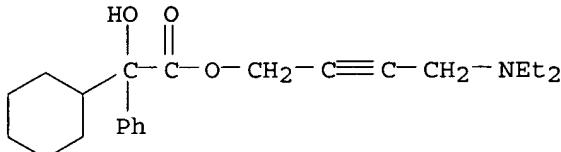
Prazosin

RL: BIOL (Biological study)

(urinary bladder contraction response to, detrusor hyperactivity treatment in relation to)

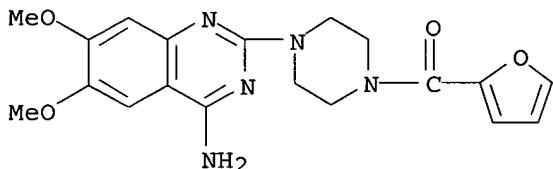
RN 5633-20-5 HCAPLUS

CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)



L69 ANSWER 64 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:233828 HCAPLUS

DOCUMENT NUMBER: 118:233828

TITLE: New basic esters of 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid endowed with spasmolytic properties: synthesis and pharmacological-pharmacokinetic evaluation

AUTHOR(S): Nardi, D.; Leonardi, A.; Pennini, R.;

Tajana, A.; Cazzulani, P.; Testa, R.

CORPORATE SOURCE: Chem. Lab., Recordati S.p.A., Milan, Italy

SOURCE: Arzneimittel-Forschung (1993), 43(1), 28-34

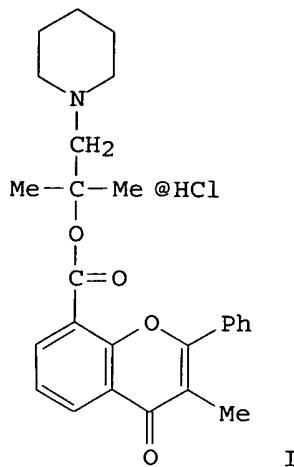
CODEN: ARZNAD; ISSN: 0004-4172

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 118:233828

GI



AB Basic esters of 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid (I) were prepared as flavoxate analogs. The activity of I esters as spasmolytics was tested and compared to flavoxate. Terflavoxate hydrochloride (II) showed affinity for muscarinic receptors but was devoid of functional antimuscarinic properties.

L69 ANSWER 65 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:223231 HCPLUS
 DOCUMENT NUMBER: 118:223231
 TITLE: Structural characterization of terflavoxate
 AUTHOR(S): Leonardi, A.; Cappelletti, R.; Nardi, D.; Giordano, F.
 CORPORATE SOURCE: Chem. Res. Dep., Recordati S.p.A., Milan, Italy
 SOURCE: Arzneimittel-Forschung (1993), 43(3), 356-62
 CODEN: ARZNAD; ISSN: 0004-4172
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Data are reported on the structural characterization of 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid 1,1-dimethyl-2-(N-piperidinyl)ethyl ester hydrochloride (terflavoxate-HCl, Rec 15/2053, CAS 86433-39-8), a new antispasmodic for the lower urinary tract. UV, IR, NMR and MS spectra fully confirmed the structure. The X-ray crystal structure determination revealed that the mol. structure consists of a rigid platform, formed by the chromone system, with two arms, the Ph group at C(2) and the ester chain at C(8). The ester chain conformation generates a small hollow where two oxygen atoms face.

L69 ANSWER 66 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:160951 HCPLUS
 DOCUMENT NUMBER: 118:160951
 TITLE: Effects of terflavoxate on stimulated contractions of urinary bladder in vitro
 AUTHOR(S): Testa, R.; Guarneri, L.; Bernasconi, P.; Angelico, P.; Ibba, M.; Poggesi, E.; Meli, A.

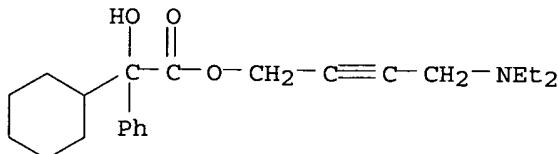
CORPORATE SOURCE: Pharmacol. Lab., Recordati S.p.A., Milan, Italy
 SOURCE: Arzneimittel-Forschung (1993), 43(2), 122-8
 CODEN: ARZNAD; ISSN: 0004-4172
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The antispasmodic activity of terflavoxate. A flavone derivative with spasmolytic properties on the urinary tract, has been studied in vitro, in comparison to the most common drugs utilized in the therapy of overactive detrusor, namely flavoxate, oxybutynin, and terodilane. Terflavoxate showed affinity for bladder (and brain) muscarinic receptors at micromolar level, however, its activity on carbachol-induced contractions of rat bladder was clearly non competitive, indicating that the compound is devoid of functional antimuscarinic properties. Moreover, the observation that unlike antimuscarinic drugs, terflavoxate inhibited by more than 50% field stimulation-induced contractions of rabbit bladder strips, indicates that mechanisms other than the anticholinergic one should be responsible for its smooth muscle relaxant properties. Terflavoxate, flavoxate, oxybutynin, and terodilane were equally effective in inhibiting the two components of K⁺-induced contractions, while nifedipine and nicardipine were more potent than the other compds., and more effective in inhibiting tonic than phasic contractions. In addition, while nifedipine and nicardipine antagonized in a competitive manner calcium-induced contractions of potassium-depolarized bladder strips, the other spasmolytics behaved as mixed antagonists. Differences in calcium antagonistic properties between nifedipine and nicardipine on one side, and terflavoxate on the other, are further demonstrated by the data on binding expts. Nevertheless, present results suggest that Ca⁺⁺-antagonistic effects are mainly responsible for terflavoxate smooth muscle relaxant properties.

L69 ANSWER 67 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1992:419777 HCPLUS
 DOCUMENT NUMBER: 117:19777
 TITLE: In vivo effects of different antispasmodic drugs on the rat bladder contractions induced by topically applied potassium chloride
 AUTHOR(S): Angelico, Patrizia; Guarneri, Luciano; Fredella, Bianca; Testa, Rodolfo
 CORPORATE SOURCE: Pharmacol. Dep., RECORDATI S.p.A., Milan, 20148, Italy
 SOURCE: Journal of Pharmacological and Toxicological Methods (1992), 27(1), 33-9
 CODEN: JPTMEZ; ISSN: 1056-8719
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The model originally proposed by Postius and Szelenyi for in vivo screening of spasmolytic compds. on the rat urinary bladder, has been modified and tested to verify its predictivity. The topically applied KCl induced reproducible contractions of the bladder that were dose dependently inhibited by i.v. administration of calcium antagonists like nifedipine, nicardipine, and verapamil. The other spasmolytics tested (oxybutynin, terodilane, flavoxate, and papaverine), showed a non-dose-related inhibition of the contractions. The in vivo potency of the calcium antagonists was related to their in vitro activity on the agonist-induced contractions of rat bladder strips, whereas the activity of the other spasmolytics appeared higher than that predicted on the basis of their in vitro efficacy. Nicardipine showed a dose-dependent inhibition of KCl-induced contractions also after oral administration, whereas oxybutynin and papaverine behaved as after i.v. administration.

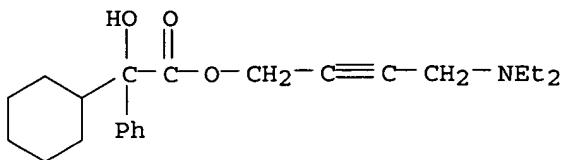
The described model represents, therefore, a good quant., and reproducible tool of screening at the bladder level only for antispasmodic drugs endowed with strong calcium antagonist activity.

- IT 5633-20-5, Oxybutynin
 RL: ANST (Analytical study)
 (potassium chloride-induced contractions of bladder inhibition by, in rat model)
- RN 5633-20-5 HCAPLUS
- CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)

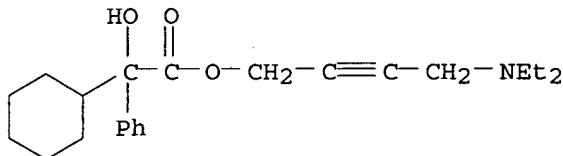


L69 ANSWER 68 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

- ACCESSION NUMBER: 1992:51138 HCAPLUS
 DOCUMENT NUMBER: 116:51138
 TITLE: Effects of oxybutynin, terodilane, and nifedipine on the cystometrogram in conscious rats with infravesical outflow obstruction
 AUTHOR(S): Guarneri, Luciano; Ibba, Marina; Angelico, Patrizia; Testa, Rodolfo
 CORPORATE SOURCE: Pharmacol. Dep., Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Pharmacological Research (1991), 24(3), 263-72
 CODEN: PHMREP; ISSN: 1043-6618
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The effects of i.v. administration of different drugs utilized in the therapy of detrusor instability have been studied in conscious catheterized female rats with infravesical outflow obstruction induced by partial urethral ligature, in comparison to normal animals. The effects of oxybutynin (1 mg/kg), terodilane (10 mg/kg), and nifedipine (1 mg/kg), were evaluated with regard to bladder capacity (BVC) and micturition pressure (MP) both in normal and obstructed rats. The effects of micturition and residual volume, as well as on spontaneous contractile activity representative of bladder instability, were also observed in obstructed rats. In normal animals, terodilane and oxybutynin induced a significant decrease in micturition pressure without changes in BVC. In obstructed rats, these drugs administered at the same doses did not induce any significant change in all the observed parameters. Nifedipine that in normal rats also reduced the MP, in obstructed animals induced an inhibition of bladder instability (about 50%) with no effects on the other cystometrograph. parameters.
 IT 5633-20-5, Oxybutynin
 RL: BIOL (Biological study)
 (detrusor muscle instability response to)
 RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butynyl ester (9CI) (CA INDEX NAME)



L69 ANSWER 69 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1992:563 HCAPLUS
 DOCUMENT NUMBER: 116:563
 TITLE: Effect of different drugs on the cystometrogram in conscious rats
 AUTHOR(S): Guarneri, Luciano; Cova, Rita; Angelico, Patrizia; Colli, Enrico; Testa, Rodolfo
 CORPORATE SOURCE: Pharmacol. Dep., Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Pharmacological Research (1991), 24(2), 175-87
 CODEN: PHMREP; ISSN: 1043-6618
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The effects on urodynamic parameters of i.v. administration of different spasmolytic drugs utilized in the therapy of detrusor instability, have been studied in conscious catheterized rats. Emperonium bromide, oxybutynin and nifedipine affected in a dose-dependent way the micturition pressure (MP), with sporadic changes in bladder volume capacity (BVC). Terodilane induced significant increases in BVC values in a wide range of doses. These changes, however, were always not dose-dependent. The drug significantly reduced MP only at the higher administered dose (10 mg/kg). Flavoxate induced increases of bladder capacity (BVC) not dependent on the administered doses, with no changes in micturition pressure (MP). Indomethacin significantly increased BVC and weakly reduced MP, but the effects were not dose-related. The effects of drugs on BVC were unrelated with the basal value of this parameter, whereas the decrease of MP seems to be related to high basal values before treatment. From a quant. point of view, cystometrog. recordings in conscious normal rats can provide comparative data among drugs acting on bladder contractility (MP) such as anticholinergics and strong calcium antagonists.
 IT 5633-20-5, Oxybutynin
 RL: BIOL (Biological study)
 (bladder detrusor muscle contraction response to, micturition in relation to)
 RN 5633-20-5 HCAPLUS
 CN Benzeneacetic acid, α -cyclohexyl- α -hydroxy-, 4-(diethylamino)-2-butyynyl ester (9CI) (CA INDEX NAME)



L69 ANSWER 70 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1990:584608 HCAPLUS

DOCUMENT NUMBER: 113:184608
 TITLE: Effects of some antidepressants on the volume-induced reflex contractions of the rat urinary bladder: lack of correlation with muscarinic receptors affinity
 AUTHOR(S): Pietra, Claudio; Poggesi, Elena; Angelico, Patrizia; Guarneri, Luciano; Testa, Rodolfo
 CORPORATE SOURCE: Pharmacol. Dep., RECORDATI S.p.A., Milan, 20148, Italy
 SOURCE: Pharmacological Research (1990), 22(4), 421-32
 CODEN: PHMREP; ISSN: 1043-6618

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB It has been suggested that tricyclic antidepressants such as imipramine, might exert their anti-enuretic action by a blockade of muscarinic receptors in the detrusor muscle of the urinary bladder . The effects of two tricyclic (imipramine and nortriptyline) and three atypical (citalopram, amineptine and mianserin) antidepressants on the micturition reflex and muscarinic receptors were studied in rats. The activity of the antidepressants was correlated to their potencies as antagonists of [³H]QNB binding to rat brain (mainly M₁ receptors) and bladder (mainly M₂ receptors) membranes, as well as antagonists of carbachol-induced contractions of rat bladder strips. Only imipramine and citalopram dose dependently inhibited the voiding contractions, whereas nortriptyline, imipramine and mianserin (in order of potency) were active both in binding studies and as competitive antagonists of carbachol-induced bladder contractions, but were inactive in inhibiting the micturition reflex. The present data seem to suggest that affinities for muscarinic receptors are unrelated to the inhibition of micturition reflex.

L69 ANSWER 71 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1990:151258 HCPLUS
 DOCUMENT NUMBER: 112:151258
 TITLE: Synthesis and anticonvulsant evaluation of 1,2-diphenylethane derivatives, potential metabolites of denzimol
 AUTHOR(S): Catto, A.; Rossi, A.; Leonardi, A.; Testa, R.; Nardi, D.
 CORPORATE SOURCE: Res. Div., Recordati S.p.A., Milan, Italy
 SOURCE: Farmaco (1989), 44(6), 595-607
 CODEN: FRMCE8; ISSN: 0014-827X

DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 112:151258

AB Twelve compds. containing the 1,2-diphenylethane group, designed as possible metabolites of denzimol and having intact or opened imidazole rings, were prepared and tested for anticonvulsant activity in mice. None of the compds. was as potent as denzimol, confirming the pivotal role of the imidazole moiety in conferring strong anticonvulsant activity to highly lipophilic aromatic alcs. and ketones. Lipophilicity tests showed that the most active compds. were the most lipophilic; however, lipophilicity was not the only parameter in determining anticonvulsant activity. Addnl. tests on two of the compds. confirmed their activity on the tonic component of seizures (inhibition of pentylenetetrazole-induced tonic seizures in mice); despite their lower potency than the reference stds. used, these 2 compds. have potential use as grand-mal anticonvulsants.

L69 ANSWER 72 OF 75 HCPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1988:527609 HCPLUS
 DOCUMENT NUMBER: 109:127609

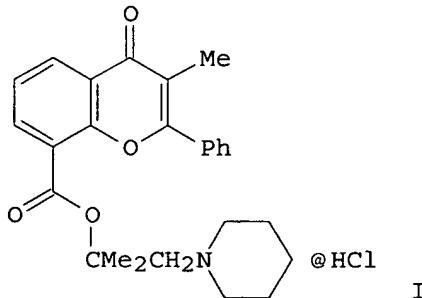
TITLE: Iron status in Sicilian subjects with
 β-thalassemia trait
 AUTHOR(S): Musumeci, S.; Romeo, M. A.; Di Gregorio, F.;
 Testa, R.; Schiliro, G.
 CORPORATE SOURCE: Dep. Pediatr., Univ. Catania, Catania, 95125, Italy
 SOURCE: Birth Defects, Original Article Series (1988), 23(5B,
 Thalassemia), 19-24
 CODEN: BTHDAK; ISSN: 0547-6844

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Male and female adults with the β-thalassemia trait (parents or relatives of children with Cooley disease) had higher blood serum Fe (31.5-36.55 vs. 19.18-19.72M) than did normal controls. The mean value of serum ferritin was higher in males than in normal controls, whereas it was in the normal range in females. Serum ferritin correlated significantly with urinary Fe excretion.

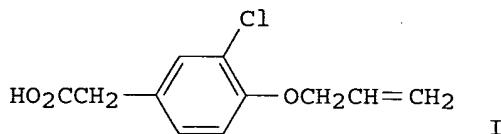
L69 ANSWER 73 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1988:522353 HCAPLUS
 DOCUMENT NUMBER: 109:122353
 TITLE: Receptor binding studies of the flavone, REC 15/2053,
 and other bladder spasmolytics
 AUTHOR(S): Abbiati, GianAlfredo; Ceserani, Roberto; Nardi, Dante;
 Pietra, Claudio; Testa, Rodolfo
 CORPORATE SOURCE: Lab. Ric., Recordati S.p.A., Milan, 20148, Italy
 SOURCE: Pharmaceutical Research (1988), 5(7), 430-3
 CODEN: PHREEB; ISSN: 0724-8741
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The flavone derivative REC 15/2053 (I), a compound with spasmolytic activity on the lower urinary tract, was examined for its in vitro interaction with neurotransmitter and opiate receptors and Ca²⁺-channel binding sites from normal rat brain. The activity of I on these receptors was compared to the most common drugs used in the management of urinary bladder disorders. I had no relevant affinity for the receptors studied, with a weak displacing activity on the 1,4-dihydropyridine binding site that was too low to justify entirely its pharmacol. activity. The low affinity for muscarinic receptors, in contrast to the reference drugs, may explain the absence of the typical anticholinergic side effects in incontinence therapy, such as dryness of the mouth, accommodation disturbances, and tachycardia.

L69 ANSWER 74 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1979:604084 HCAPLUS
 DOCUMENT NUMBER: 91:204084
 TITLE: Methods for evaluation of urinary excretion parameters of alclofenac after intramuscular administration of its water soluble lysine salt in man
 AUTHOR(S): Testa, Rodolfo; Latini, Roberto
 CORPORATE SOURCE: Lab. Ric. Farmacol., Ist. Franco Tosi, Milan, Italy
 SOURCE: European Journal of Drug Metabolism and Pharmacokinetics (1979), 4(2), 91-6
 CODEN: EJDPD2; ISSN: 0398-7639
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The urinary excretion data after i.m. administration of water soluble Alclofenac lysine salt (I lysine salt) [59960-34-8] were analyzed by the techniques suggested by Niebergall, Wagner, Martin and Cummings. All methods used gave similar ests. of both DU ∞ (amount of drug ultimately excreted) and Kel (overall elimination rate constant) with exception of the "sigma minus" method when DU ∞ obtained by "Rate Method" was utilized. Niebergall's method was preferred on the basis that it provided an accurate estimation of both DU ∞ and Kel. These parameters, evaluated after administration of I lysinate, resulted in agreement with previously reported data obtained after administration of different pharmaceuticals of acidic drugs.

L69 ANSWER 75 OF 75 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1970:443819 HCAPLUS
 DOCUMENT NUMBER: 73:43819
 TITLE: Magnesium. Physiopathology and clinical study
 AUTHOR(S): Zaffiri, O.; Centi, R.; Contratti, V.; Leonardi, A.
 CORPORATE SOURCE: Serv. Anest. Rianim., Osp. Magg. Trieste, Trieste, Italy
 SOURCE: Minerva Anestesiologica (1969), 35(12), 1309-12
 CODEN: MIANAP; ISSN: 0375-9393
 DOCUMENT TYPE: Journal
 LANGUAGE: Italian

AB The i.v. administration of Mg salts must be practiced very slowly (1.5 ml/min of a 10% solution) since the plasma level of Mg rises immediately and remains high for at least 30 min and is accompanied by signs of hypotension, collapse, and respiratory depression with neuromuscular block.

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